IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

14 CV 0866

LIGIA VANESSA CHAPETON and
GARY SEYMOUR,

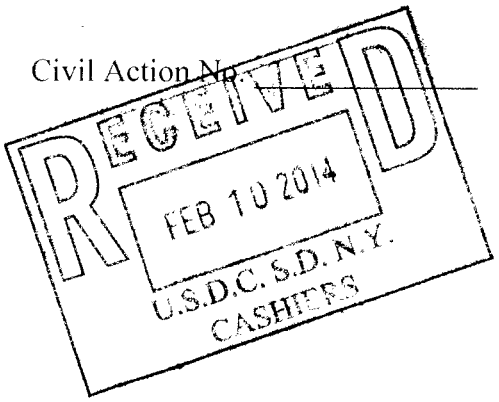
Plaintiffs,

-against-

MEDTRONIC INC., MEDTRONIC SOFAMOR DANEK, USA, INC., and ROGER HARTL, M.D,

Defendants.

Civil Action No.



NOTICE OF REMOVAL

Medtronic, Inc. ("Medtronic") and Medtronic Sofamor Danek USA, Inc. ("MSD") (collectively, the "Medtronic Defendants"), by and through their undersigned counsel, hereby provide notice pursuant to 28 U.S.C. § 1446 of the removal of the above-captioned case from the Supreme Court of the State of New York, County of New York to the United States District Court for the Southern District of New York. The grounds for removal are as follows:

1. Plaintiffs commenced this action by filing a summons with notice on or about December 6, 2013 in the Supreme Court of the State of New York, County of New York, and the case was docketed at 161291/2013. Plaintiff served the Medtronic Defendants with copies of the summons with notice on December 9, 2013. The Medtronic Defendants appeared and served a demand for complaint on December 23, 2013.

2. Plaintiffs filed a verified complaint (the "Complaint") on January 21, 2014. A true and correct copy of the state court pleadings are attached hereto as Exhibit A.

3. Roger Hartl, M.D. also is named as a defendant in the Complaint. Counsel for Roger Hartl, M.D. has advised counsel for the Medtronic Defendants that Roger Hartl, M.D. consents to removal of this case to federal court. A true and correct copy of Roger Hartl, M.D.'s notice of consent is attached hereto as Exhibit B.

4. No other pleadings or papers have been filed in this litigation.

5. Under 28 U.S.C. § 1446(b), this Notice of Removal must be filed within 30 days of service of the Complaint upon the Medtronic Defendants. Since the Medtronic Defendants are filing this Notice on February 10, 2014, removal is timely.

6. Concurrent with the filing of this Notice, the Medtronic Defendants are serving this Notice on Plaintiffs' counsel and filing a copy of the Notice with the Supreme Court of the State of New York, County of New York. Venue is proper in this Court pursuant to 28 U.S.C. §§ 112(b) and 1441(a), because the United States District Court for the Southern District of New York is the federal judicial district embracing the Supreme Court of the State of New York, County of New York, where this action was originally filed.

7. The time for the Medtronic Defendants to answer, move, or otherwise plead with respect to the Complaint has not yet expired.

8. By filing a Notice of Removal in this matter, the Medtronic Defendants do not waive their rights to object to service of process, the sufficiency of process, jurisdiction over the person, or venue, and the Medtronic Defendants specifically reserve all defendants' rights to assert any defenses and/or objections to which they may be entitled.

9. As shown below, this case is removable to federal court based on federal question jurisdiction under 28 U.S.C. § 1331.

FEDERAL-QUESTION JURISDICTION

10. This case is removable based on federal question jurisdiction. Under 28 U.S.C. § 1331, the district courts "have original jurisdiction of all civil actions arising under the Constitution, laws, or treaties of the United States." 28 U.S.C. § 1331.

11. Plaintiffs allege that Plaintiff Ligia Vanessa Chapeton was injured by her physician's alleged off-label use of the Medtronic Defendants' Infuse Bone Graft/LT-Cage Lumbar Tapered Fusion Device ("Infuse"). *See, e.g.*, Compl. ¶¶ 16, 347.

12. Federal regulation of medical devices is governed by the Medical Device Amendments of 1976 (MDA), 21 U.S.C. § 360c, *et seq. See Riegel v. Medtronic, Inc.*, 552 U.S. 312, 316 (2008). The MDA establishes three classes of increasingly stringent federal oversight. *Id.* at 316-17.

13. "Class I, which includes such devices as elastic bandages and examination gloves, is subject to the lowest level of oversight." *Id.* at 316.

14. "Class II, which includes such devices as powered wheelchairs and surgical drapes, is subject in addition to 'special controls' such as performance standards and postmarket surveillance measures." *Id.* at 316-17 (citing § 360c(a)(1)(B)).

15. Only devices that "support[] or sustain[] human life" or "present[] a potential unreasonable risk of illness or injury" are designated "Class III" devices. 21 U.S.C. § 360c(a)(1)(C)(ii). Class III devices "receiv[e] the most federal oversight" and innovative Class III devices must go through "a rigorous regime of premarket approval" before they may be brought to market. *Riegel*, 552 U.S. at 317.

16. Infuse is a Class III medical device whose design, manufacturing method, and labeling were specifically approved by the Food and Drug Administration (FDA) pursuant to the agency's Premarket Approval (PMA) process. *See* Compl. ¶¶ 28-29; *see also* U.S. Food & Drug Admin., *Premarket Approval (PMA)—Infuse Bone Graft/LT-Cage Lumbar Tapered Fusion Device*, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=11719.[1]

17. The PMA process for Class III devices is the most exacting form of FDA review. To obtain FDA approval via the PMA process, a manufacturer

> must submit a detailed PMA application that contains full reports of all investigations of the safety and effectiveness of the device; a full statement of the components, ingredients, properties, and principles of operation of the device; a full description of the methods used in the manufacture and processing of the device; information about performance standards of the device; samples of the device; specimens of the proposed labeling for the device; and any other relevant information.

Riegel v. Medtronic, Inc., 451 F.3d 104, 109 (2d Cir. 2006) (citing 21 U.S.C. § 360e(c)), *aff'd*, 552 U.S. 312 (2008). The FDA rigorously scrutinizes PMA applications, "'weig[hing] any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.'" *Riegel*, 552 U.S. at 318 (quoting 21 U.S.C. § 360c(a)(2)(C)). "The FDA spends an average of 1,200 hours reviewing each application" and "grants premarket approval only if it finds there is a 'reasonable assurance' of the device's 'safety and effectiveness.'" *Id.* at 318 (quoting 21 U.S.C. § 360e(d)).

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[1] This web page is part of the FDA's public database of premarket approvals, which is accessible at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. This Court may take judicial notice of the fact of Infuse's premarket approval because the FDA's public website is a database maintained by the FDA in the normal course of its business and reflects final agency action. Fed. R. Evid. 201; *see, e.g.*, *Funk v. Stryker Corp.*, 631 F.3d 777, 783 (5th Cir. 2011) (affirming judicial notice of PMA approval); *Gross v. Stryker Corp.*, 858 F. Supp. 2d 466, 481 n.26 (W.D. Pa. 2012) (taking judicial notice of FDA approval documents).

18. "Once a device has received premarket approval, the MDA forbids the manufacturer to make, without FDA permission, changes in design specifications, manufacturing processes, labeling, or any other attribute, that would affect safety or effectiveness." *Riegel*, 552 U.S. at 319 (citing 21 U.S.C. § 360e(d)(6)(A)(i)).

19. Section 360k(a) of the MDA expressly preempts any state-law claim that would impose a requirement that is "different from, or in addition to" those imposed by the FDA. 21 U.S.C. § 360k(a); *see Riegel*, 552 U.S. at 321-28. Through this provision, Congress expressly preempted state-law tort claims challenging the design, manufacture, or labeling of a medical device previously approved by the FDA via the PMA process.

20. This preemption provision has a narrow exception for claims that "'parallel,' rather than add to, federal requirements." *Riegel*, 552 U.S. at 330. To be "parallel," a state-law requirement must be "identical" to a federal requirement. *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 (1996).

21. Plaintiffs' causes of action allege that the Medtronic Defendants' purported activities were prohibited by "federal law" (Compl. ¶¶ 38, 77), and "violated the[] FDCA statutes and accompanying regulations" (*id.* ¶ 127; *see also id.* ¶¶ 128-129). The federal statutes and regulations relied on by Plaintiffs include 21 C.F.R. §§ 201.100, 201.128, 202.1, 801.4, 801.5, 803, 803.50(a), 814.39(a), 814.80, 814.84(b)(2), 820.1(a), 820.3(z)(x), 820.5, 820.22, 820.30, 820.100, 820.160(a), 820.170(a), and 820.198(a), as well as 21 U.S.C. §§ 321(k), 321(m), 321(n), 331(a), 331(b), 331(k), 351(f), 352(a), 352(f), 352(q), 360aaa, 360aaa-1, 360c, 360e, 360h, and 360i(a), and also Fed. Reg. 14286 (Mar. 16, 2000) and 59 Fed. Reg. 59821 (Nov. 18, 1994). *See, e.g.*, Compl. ¶¶ 44-124.

22. Thus, while Plaintiffs' claims against the Medtronic Defendants are nominally labeled as claims under state law, each claim is necessarily predicated on alleged breaches of duties imposed by ***federal*** law and challenges the safety and effectiveness of a device subject to pervasive federal regulation and administrative oversight. In fact, Plaintiffs cannot state a claim and cannot prevail without demonstrating a violation of relevant federal requirements on the Infuse device that is causally linked to the alleged injuries. Accordingly violation of federal law is a critical and indispensable element of Plaintiffs' claims and burden of proof.

23. A claim may arise under federal law in either of two ways. In many cases, "federal-question jurisdiction is invoked . . . by plaintiffs pleading a cause of action created by federal law." *Grable & Sons Metal Prods., Inc. v. Darue Eng'g & Mfg.*, 545 U.S. 308, 312 (2005). In other cases, although the plaintiff's cause of action is nominally created by state law, "federal-question jurisdiction will lie over state-law claims that implicate significant federal issues." *Id.* This second form of federal-question jurisdiction "captures the commonsense notion that a federal court ought to be able to hear claims recognized under state law that nonetheless turn on substantial questions of federal law, and thus justify resort to the experience, solicitude, and hope of uniformity that a federal forum offers on federal issues." *Id.*

24. When evaluating whether a federal statute creates a substantial federal interest giving rise to federal-question jurisdiction over claims pleaded under state law, the Supreme Court has "disclaimed the adoption of any bright-line rule." *Id.* at 317. "Instead, the question is, does a state-law claim necessarily raise a stated federal issue, actually disputed and substantial, which a federal forum may entertain without disturbing any congressionally approved balance of federal and state judicial responsibilities." *Grable*, 545 U.S. at 314; *see also MDS (Canada) Inc. v. Rad Source Technologies, Inc.*, 720 F.3d 833, 841 (11th Cir. 2013); *Mikulski v. Centerior*

Energy Corp., 501 F.3d 555, 568 (6th Cir. 2007) (en banc); *Broder v. Cablevision Sys. Corp.*, 418 F.3d 187, 194 (2d Cir. 2005). This question requires courts to make "'sensitive judgments about congressional intent.'" *Grable*, 545 U.S. at 318; *accord Mikulski*, 501 F.3d at 561 ("our inquiry is ultimately one of congressional intent").

25. By enacting the MDA, Congress both recognized and reinforced a substantial federal interest in the regulation of PMA-approved Class III medical devices. Indeed, as the Supreme Court explained in *Riegel*, the very purpose of the MDA was to "swe[ep] back some state obligations and impose[] a regime of detailed federal oversight." 552 U.S. at 316. Just as Congress took the regulation of medical devices out of the hands of state legislatures and entrusted it instead to the exclusive authority of an expert federal agency, namely the FDA, so too Congress presumably wanted the litigation of medical device claims involving innovative Class III medical devices, the most complex devices subject to the most detailed federal oversight, to be removable from state courts so that such litigation could proceed under the eye of the federal judiciary. Indeed, it would be peculiar for Congress to have "imposed a regime of detailed federal oversight" (*id.*) while at the same time preventing claims predicated on the purported violation of federal requirements established by that regime to be removed to federal court.

26. For this reason, a district court in Tennessee considering allegations and claims nearly identical to those made by Plaintiffs here recently concluded that because these "claims undoubtedly require this Court to examine federal law, and, even more specifically, examine federal requirements imposed by the FDA through the premarket approval process," they are

properly subject to "federal question jurisdiction under the substantial-federal-question doctrine." *Jenkins v. Medtronic, Inc.*, --- F. Supp. 2d ----, 2013 WL 6172234, at *3 (M.D. Tenn. 2013).[2]

27. Although a plaintiff suing for an injury allegedly caused by an FDA-approved medical device may still attempt to recite a cause of action nominally recognized under state law, to plead and prove a non-preempted "parallel" claim, "[t]he plaintiff must be suing for conduct that violates the FDCA (or else his claim is expressly preempted by § 360k(a))." *Bryant v. Medtronic, Inc.*, 623 F.3d 1200, 1204 (8th Cir. 2010). Thus, for a claim to escape express preemption, the duty at issue must necessarily be one imposed by federal law. Because "Plaintiffs cannot prevail on their claims unless they prove that Defendants violated requirements imposed by the FDA on the Infuse" device (*Jenkins*, 2013 WL 6172234, at *5), the resolution of such claims necessarily "implicate[s] significant federal issues" and "turn[s] on substantial questions of federal law" (*Grable*, 545 U.S. at 312). *Accord Bowdrie v. Sun Pharm. Indus.*, 2012 WL 5465994, at *3 (E.D.N.Y. 2012) (holding that a state-law negligence and product-liability action against generic drug manufacturers "necessarily raises a federal question" because, to avoid preemption, the plaintiffs were required to prove a violation of the "ongoing federal duty of sameness" under the Hatch-Waxman Act).

28. As the Court concluded in *Jenkins*, there can be no question that the federal question raised by Plaintiffs' purportedly parallel claims is substantial "because ... the Court must address an important federal question that deals specifically ... with federal regulations and

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[2] The Medtronic Defendants acknowledge that other district courts have declined to find federal question jurisdiction in other cases involving Infuse. *See Mooney v. Henkin*, No. 13-cv-3213 (Feb. 9, 2014); *Dillon v. Medtronic, Inc.*, No. 13-cv-105 (E.D. Ky. Dec. 20, 2013); *Goade v. Medtronic*, No. 13-cv-5123 (W.D. Mo. Dec. 3, 2013); *David v. Medtronic, Inc.*, No. 13-cv-4441 (C.D. Cal. Aug. 6, 2013). The Medtronic Defendants respectfully submit that these decisions were erroneous and that the district court's decision in *Jenkins* finding federal question jurisdiction is correct because it more faithfully adheres to the test set forth in *Grable*.

requirements regarding a highly regulated device." 2013 WL 6172234, at *6. To begin with, the question whether Plaintiffs can establish the violation of a federal duty that parallels their state-law claims is likely to be "dispositive of this case." *Mikulski*, 501 F.3d at 571; *see, e.g.*, *Mitchell v. Bank of Am., N.A.*, 2010 WL 3340486, at *2-3 (M.D. Fla. 2010) (finding a substantial federal question where plaintiffs' civil conspiracy claim "necessarily depends on . . . Defendants' alleged violation of the Fair Debt Collection Practices Act"); *cf. Landers v. Morgan Asset Mgmt., Inc.*, No. 08-2260, 2009 WL 962689, at *8 (W.D. Tenn. Mar. 31, 2009) (finding a substantial federal question where plaintiffs' negligence claim necessarily "depends on a finding that the Defendants did not meet the standard of care imposed by federal . . . law"); *Avila-Gonzalez v. Barajas*, 2006 WL 643297, at *1 (M.D. Fla. 2006) (finding a substantial federal question where plaintiffs' contract claim "turn[ed] on interpretation of terms dictated by federal statutes and regulations," and there was a substantial federal interest in "seeing that businesses honor the obligations they assume in order to obtain [federal] governmental approval of their activities"). Indeed, Congress, through the MDA's express preemption clause, has specifically barred claims against medical device manufacturers including the sort of claims asserted by Plaintiffs ***unless*** Plaintiffs can plead and prove the violation of a parallel federal-law duty. Moreover, the enforcement of the federal duties at issue here is committed to the pervasive oversight of the FDA, a federal agency. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 (2001) (describing the "variety of enforcement options" available to the FDA). In addition, the involvement of a federal agency, such as the involvement of the FDA in the regulation of Class III medical devices, is a factor supporting the substantiality of the federal interest in a case. *Mikulski*, 501 F.3d at 570. Regulation of the design and labeling of PMA-approved medical devices "is in the first instance, and primarily, federal." *Cf. Bowdrie*, 2011 WL 5465994, at *4.

29. Two features of the MDA distinguish litigation over Class III medical devices from the claim in *Merrell Dow Pharmaceuticals, Inc. v. Thompson*, 478 U.S. 804 (1985), which held that the Food, Drug, and Cosmetics Act (FDCA) did not provide a federal forum for misbranding claims against prescription drugs. First, in *Merrell Dow* it was of "primary importance" that the FDCA provided "no federal cause of action ***and no preemption of state remedies*** for misbranding." *Grable*, 545 U.S. at 318 (emphasis added).[3] The Court deemed that combination "an important clue" as to Congress's intent. *Id.* For Class III medical devices, by contrast, the MDA ***expressly preempts*** state-law remedies. *See* 21 U.S.C. § 360k(a); *see also Wyeth v. Levine*, 555 U.S. 555, 567 (2009) ("when Congress enacted an express pre-emption provision for medical devices in 1976, it declined to enact such a provision for prescription drugs" (citing 21 U.S.C. § 360k(a)). There is, therefore, no need under the MDA for courts to collect "clues" to Congress's intent with respect to the regulation of medical devices, and, in particular, Congress's intent to sweep back state laws with respect to Class III medical devices. As the Supreme Court has authoritatively recognized, "the text of the statute" evinces Congress's intent to displace "the tort law of 50 States" and "impose[] a regime of detailed federal oversight." *Riegel*, 552 U.S. at 316, 326.

30. Second, unlike in *Merrell Dow*, federal jurisdiction over claims concerning Class III medical devices that have received premarket approval from the FDA would not risk opening the federal courts to a flood of litigation. *Merrell Dow* was concerned that opening a federal forum to all litigation involving any aspect of the FDCA "would have attracted a horde of original filings and removal cases raising other state claims with embedded federal issues." *Grable*, 545 U.S. at 318. There is no such danger here. The federal interest recognized by the

[3] *Grable* is careful to note that "the absence of a federal private right of action" is "not dispositive of" whether Congress intended to provide access to a federal forum. 545 U.S. at 318.

MDA is implicated ***only*** by claims concerning Class III medical devices that have received premarket approval from the FDA. Such devices constitute a small fraction of a small subset of medical devices. To start, only devices that "support[] or sustain[] human life" or "present[] a potential unreasonable risk of illness or injury" are designated "Class III" devices. 21 U.S.C. § 360c(a)(1)(C)(ii). Only a relatively small number of medical devices fall into that category. And of those that do, "only a small percentage" are subject to the premarket approval process. *Smith v. Phoenix Seating Systems, LLC*, 894 F. Supp. 2d 1088, 1097 (S.D. Ill. 2012). Indeed, "[t]he vast majority of Class III medical devices . . . reach the market without ever going through the rigorous PMA process." *Riegel*, 451 F.3d at 111.[4] Thus, there is no danger that federal jurisdiction over claims concerning Class III medical devices with premarket approval will have any significant impact on the workload of the federal courts; rather, it "will portend only a microscopic effect on the federal-state division of labor." *Grable*, 545 U.S. at 315; *accord Jenkins*, 2013 WL 6172234, at *7 (concluding that "the state-federal jurisdictional balance" would be "untouched" by exercising "federal question jurisdiction" over claims identical to Plaintiff's). Federal jurisdiction over this narrow class of cases concerning PMA-approved Class III medical devices under the MDA is therefore fully "consistent with congressional judgment about the sound division of labor between state and federal courts." *Grable*, 545 U.S. 313; *see Jenkins*, 2013 WL 6172234, at *7.

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[4] "Most new Class III devices enter the market through" what "is known as the § 510(k) process," a far less rigorous process that does not trigger preemption under § 360k(a). *Riegel*, 552 U.S. at 317. "In 2005, for example, the FDA authorized the marketing of 3,148 devices under § 510(k) and granted premarket approval to just 32 devices." *Id.* (citing P. Hutt, R. Merrill, & L. Grossman, *Food and Drug Law* 992 (3d ed. 2007). "In other words, in 2005, approximately ninety-nine percent of such devices went through the § 510(k) process and only ***one percent*** went through the PMA process." *Riegel*, 451 F.3d at 112 (emphasis in original). The numbers remain similar today. In 2011, only 51 devices received premarket approval. *See* http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/default.htm.

31. By enacting the MDA, Congress declared that medical devices are to be governed exclusively by requirements of federal law that are administered and enforced exclusively by the expert decisions of a federal agency. There can be little question that Plaintiff's tort claims, which challenge the safety and effectiveness of such a device and invoke federal statutory and regulatory requirements for Class III medical devices, implicate substantial federal interests that call for the availability of jurisdiction in a federal forum. "The regulations and requirements of the safety and effectiveness of a Class III, premarket approved device belong under the scope of federal question jurisdiction." *Jenkins*, 2013 WL 6172234, at *7.

32. Accordingly, this Court has federal question jurisdiction under 28 U.S.C. § 1331, and this case is removable under 28 U.S.C. § 1441.

WHEREFORE, Notice is given that this action is removed from the Supreme Court of the State of New York, County of New York to the United States District Court for the Southern District of New York.

Dated: February 10, 2014.

Respectfully submitted,

PEPPER HAMILTON, LLP

By: _____

Samuel J. Abate, Jr.
The New York Times Building
620 Eighth Avenue
New York, New York 10018
(212) 808-2700

Counsel for Defendants Medtronic, Inc. and Medtronic Sofamor Danek USA, Inc.

CERTIFICATE OF SERVICE

I, Samuel J. Abate, Jr., an attorney, certify that I caused a copy of the attached Defendants Medtronic, Inc. and Medtronic Sofamor Danek USA, Inc.'s Notice of Removal to be served by sending the same by U.S. Mail, first class, postage prepaid on February 10th , 2014, addressed to the following:

Wendy R. Fleishman
Lieff, Cabraser, Heimann & Bernstein, LLP
250 Hudson Street, 8th Floor
New York, NY 10013

Samuel J. Abate, Jr

EXHIBIT A

FILED: NEW YORK COUNTY CLERK 12/06/2013 INDEX NO. 161291/2013
NYSCEF DOC. NO. 1 RECEIVED NYSCEF: 12/06/2013

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF NEW YORK

LIGIA VANESSA CHAPETON, an individual, and GARY SEYMOUR, an individual Plaintiffs, -against- MEDTRONIC, INC., a Minnesota corporation; MEDTRONIC SOFAMOR DANEK, USA, INC., a Tennessee corporation; ROGER HARTL, M.D., an individual Defendants.	INDEX NO. **SUMMONS WITH NOTICE**

To the Persons Named as Defendants Above:

PLEASE TAKE NOTICE THAT YOU ARE HEREBY SUMMONED to appear in this action by serving a notice of appearance on the Plaintiffs at the address set forth below within 20 days after the service of this Summons (not counting the day of service itself), or within 30 days after service is complete if the summons is not delivered personally to you within the State of New York.

YOU ARE HEREBY NOTIFIED THAT should you fail to answer or appear, a judgment will be entered against you by default for the relief demanded below.

Dated: December 6, 2013

Respectfully submitted,

LIEFF CABRASER HEIMANN & BERNSTEIN, LLP

By: */e/ Wendy R. Fleishman*
WENDY R. FLEISHMAN (WF3017)

Daniel R. Leathers (DL4995)
LIEFF CABRASER HEIMANN & BERNSTEIN, LLP
250 Hudson Street, 8th Floor
New York, NY 10013
Telephone: (212) 355-9500
Facsimile: (212) 355-9592

Kent L. Klaudt (*Pro Hac Vice Anticipated*)
Cecilia Han (*Pro Hac Vice Anticipated*)
LIEFF CABRASER HEIMANN & BERNSTEIN, LLP
275 Battery Street, 29th Floor
San Francisco, CA 94111
Telephone: (415) 956-1000
Facsimile: (415) 956-1008

Attorneys for Plaintiffs

Defendants' Addresses:

Defendant MEDTRONIC, INC.
Principal place of business: 710 Medtronic Parkway
Minneapolis, MN 55432

c/o Registered Agent: CT CORPORATION SYSTEM
111 Eighth Avenue
New York, NY 10011

Defendant MEDTRONIC SOFAMOR DANEK, USA, INC.
Principal place of business: 2600 Sofamor Danek Drive
Memphis, TN 38132

c/o Registered Agent: CT CORPORATION SYSTEM
111 Eighth Avenue
New York, NY 10011

Defendant ROGER HARTL, M.D.
Principal place of business: Weill Cornell Medical College
525 East 68th Street
STARR-651 - Box 99
New York, NY 10065

Notice:

The nature of this action is: Personal injury/Product Liability, Medical Malpractice

The relief sought is: Compensatory damages, punitive damages, attorneys' fees and costs

Should Defendants fail to appear herein, judgment will be entered by default for the sum of $20,000,000.00 with interest and the costs from the date of the filing of this action.

Venue: Plaintiffs designates New York County as the place of trial. The basis of this designation is Plaintiffs' residence in New York County.

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF NEW YORK

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LIGIA VANESSA CHAPETON, an individual, and GARY SEYMOUR, an individual,

Index No. 161291/2013

Plaintiffs,

-against-

MEDTRONIC, INC., a Minnesota corporation; MEDTRONIC SOFAMOR DANEK USA, INC., a Tennessee corporation; ROGER HARTL, M.D., an individual

NOTICE OF APPEARANCE AND DEMAND FOR A VERIFIED COMPLAINT

Defendants.

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NOTICE OF APPEARANCE

PLEASE TAKE NOTICE that Pepper Hamilton LLP, has been retained as counsel to appear on behalf of Medtronic, Inc. and Medtronic Sofamor Danek USA, Inc., defendants in the above-captioned matter, and hereby requests and demands that the firm be served with all pleadings, discovery, and all other litigation documents and materials, addressed to the defendants at the address provided below. Defendants do not hereby waive any defenses available to them by statute, common law, contract, warranty or otherwise, by appearing through this Notice. This includes all applicable jurisdictional defenses.

DEMAND FOR A VERIFIED COMPLAINT

PLEASE TAKE FURTHER NOTICE, that pursuant to CPLR 3012(b), Defendants hereby demand that a Verified Complaint and all prior notices in the above-captioned action be

served on counsel at the address indicated below within twenty (20) days of the service of this demand.

Dated: New York, New York
December 23, 2013

PEPPER HAMILTON, LLP

By: _____
Samuel J. Abate, Jr.
The New York Times Building
620 Eighth Avenue
New York, New York 10018
(212) 808-2700

Attorneys for Defendants Medtronic, Inc. and Medtronic Sofamor Danek USA, Inc.

TO: LIEFF CABRASER HEIMANN & BERNSTEIN, LLP
250 Hudson St., 8th Floor
New York, NY 10013

LIEFF CABRASER HEIMANN & BERNSTEIN, LLP
275 Battery Street, 29th Floor
San Francisco, CA 94111

Attorneys for Plaintiff

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF NEW YORK

----------x

LIGIA VANESSA CHAPETON, an individual, and GARY SEYMOUR, and individual,

Index No. 161291/2013

Plaintiffs,

-against-

MEDTRONIC, INC., a Minnesota corporation; MEDTRONIC SOFAMOR DANEK USA, INC., a Tennessee corporation; ROBERT HARTL, M.D., an individual,

AFFIDAVIT OF SERVICE

Defendants.

----------x

The undersigned, being duly sworn, deposes and says that she is over the age of 18 years, and is not a party to this action.

That on the 23rd day of December, 2013, she caused to be served the within NOTICE OF APPEARANCE AND DEMAND FOR A VERIFIED COMPLAINT by first class mail upon:

Lieff Cabraser Heimann & Bernstein, LLP
250 Hudson St., 8th Floor
New York, NY 10013

Lieff Cabraser Heimann & Bernstein, LLP
275 Battery Street, 29th Floor
San Francisco, CA 94111

by depositing a true copy of same, securely enclosed in a postpaid properly addressed wrapper, in an official depository under the exclusive care and custody of the United States Postal Service.

Marie A. Ramos

Sworn to and subscribed before me
this 30th day of December, 2013.

Notary Public

York

FILED: NEW YORK COUNTY CLERK 01/21/2014 INDEX NO. 161291/2013
NYSCEF DOC. NO. 4 RECEIVED NYSCEF: 01/21/2014

SUPREME COURT OF THE STATE OF NEW YORK

COUNTY OF NEW YORK

LIGIA VANESSA CHAPETON, an individual, and GARY SEYMOUR, an individual

Plaintiffs,

-against-

MEDTRONIC, INC., a Minnesota corporation; MEDTRONIC SOFAMOR DANEK, USA, INC., a Tennessee corporation; ROGER HARTL, M.D., an individual

Defendants.

Date Filed: December 6, 2013

INDEX No. 161291/2013

SUMMONS

Plaintiffs designate - New York County as the place of trial

The basis of the venue – Plaintiffs' residence and location of all alleged tortious conduct

Defendants reside at – Defendant MEDTRONIC, INC.
710 Medtronic Parkway
Minneapolis, MN 55432

Defendant MEDTRONIC SOFAMOR DANEK, USA, INC.
2600 Sofamor Danek Drive
Memphis, TN 38132

Defendant ROGER HARTL, M.D.
Weill Cornell Medical College
525 East 68th Street
STARR-651 - Box 99
New York, NY 10065

To the Above Named Defendants:

You are hereby summoned to answer the Civil Action Complaint in this action and to serve a copy of your Answer, or, if the Complaint is not served with this Summons, to serve a Notice of Appearance, on Plaintiffs' Attorneys within (20) days after the service of this Summons, exclusive of the day of service (or within 30 days after the service is complete if this summons is not personally delivered to you within the State of New York); and in case of your failure to appear or answer, judgment will be taken against you by default for the relief demanded in the Complaint.

Dated: January 21, 2014

Respectfully submitted,

LIEFF, CABRASER, HEIMANN & BERNSTEIN, LLP

By: */s Wendy R. Fleishman*
Wendy R. Fleishman

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Defendants' Addresses:

Defendant MEDTRONIC, INC.
Principal place of business: 710 Medtronic Parkway
Minneapolis, MN 55432

c/o Registered Agent: CT CORPORATION SYSTEM
111 Eighth Avenue
New York, NY 10011

Defendant MEDTRONIC SOFAMOR DANEK, USA, INC.
Principal place of business: 2600 Sofamor Danek Drive
Memphis, TN 38132

c/o Registered Agent:

CT CORPORATION SYSTEM
111 Eighth Avenue
New York, NY 10011

Defendant ROGER HARTL, M.D.
Place of business:

Weill Cornell Medical College
525 East 68th Street
STARR-651 - Box 99
New York, NY 10065

SUPREME COURT OF THE STATE OF NEW YORK

COUNTY OF NEW YORK

LIGIA VANESSA CHAPETON, an individual, and GARY SEYMOUR, an individual Plaintiffs, -against- MEDTRONIC, INC., a Minnesota corporation; MEDTRONIC SOFAMOR DANEK, USA, INC., a Tennessee corporation; ROGER HARTL, M.D., an individual Defendants.	INDEX No. 161291/2013 **VERIFIED COMPLAINT** **JURY TRIAL DEMANDED**

Plaintiffs LIGIA VANESSA CHAPETON and GARY SEYMOUR ("Plaintiffs"), by and through their counsel, allege as follows against Defendants MEDTRONIC, INC. and MEDTRONIC SOFAMOR DANEK, USA, INC and .:

INTRODUCTION

1. This case involves a spinal surgery in which a bio-engineered bone growth protein known as Infuse® was implanted in Plaintiff LIGIA VANESSA CHAPETON in an off-label manner.

2. Infuse® is the trade name for rhBMP-2, bone morphogenetic protein. In 2002 the Federal Drug Administration ("FDA") approved a Class III medical device that included Infuse® as a component of the device. The other required component of the device consisted of a hollow metal cylinder called an LT-CAGE™. The device was approved for only one specific type of spine surgery - one level fusion in the lumbar spine that is performed through the abdomen (anterior).

3. Infuse® was designed and manufactured by Defendants MEDTRONIC, INC., and MEDTRONIC SOFAMOR DANEK, USA, INC. (collectively "the MEDTRONIC Defendants" or "MEDTRONIC") and was illegally and improperly promoted and sold by MEDTRONIC for off-label uses in spine surgery patients, including in LIGIA VANESSA CHAPETON.

4. Infuse® is not, and never has been, approved for use in posterior approach lumbar spine surgeries or for use in multiple levels in the lumbar spine. These surgeries are thus "off-label." Despite this lack of FDA approval, Infuse® was improperly promoted by MEDTRONIC to be used off-label for posterior approach lumbar spine fusions, and without an LT-Cage™.

5. MEDTRONIC recklessly and/or intentionally minimized and/or downplayed the risks of serious side effects related to the use of Infuse®, and especially those risks related to the off-label use of Infuse®, including but not limited to the risk of ectopic or uncontrolled bone growth.

6. After the FDA approved the Infuse® combination device, MEDTRONIC also failed to warn the agency of the growing number of adverse events due to the off label uses of Infuse® and related risks.

7. MEDTRONIC manufactured, marketed and sold Infuse®, which was defectively designed in that it had never been approved by the FDA. The defective design consisted of the bone morphogenetic protein alone. Thus, this is a different design from what the FDA approved. Accordingly, the FDA never weighed the risks versus the benefits on the misbranded design manufactured, marketed and sold by MEDTRONIC.

8. Patients' spine surgeons, including Plaintiff's surgeon, were persuaded by MEDTRONIC and by MEDTRONIC's consultant "opinion leaders," who are paid physician promoters, to expand their use of Infuse® for off-label uses.

9. When Infuse® is used off-label, it can cause severe injuries to the patient, including Infuse®-induced bone overgrowth and other complications that often necessitate risky, painful, and costly revision surgeries, which may not cure the problems caused by the Infuse® use.

10. This uncontrolled bone growth (also known as "ectopic" or "exuberant" bone growth) can result in severe damage to or compression of the surrounding neurologic structures in the spine, and bone can grow onto or around the spinal cord or the spinal nerve roots. When nerves are compressed by such excessive bone growth, a patient can experience, among other adverse events, intractable pain, paralysis, spasms, and the need for revision surgery.

11. When Infuse® is used off-label, it can cause or contribute to other serious injuries and complications, including extreme inflammatory reactions, chronic radiculitis, retrograde ejaculation, sterility, osteolysis (bone resorption), displacement or migration of the spacer cage, pseudoarthrosis, and worse overall outcomes.

12. Notwithstanding overwhelming and substantial evidence (including MEDTRONIC-sponsored studies) demonstrating these increased risks of adverse reactions from off-label use of Infuse®, MEDTRONIC recklessly and/or intentionally misrepresented, minimized, downplayed, disregarded, and/or completely omitted these off-label risks while promoting Infuse® to spine surgeons for off-label uses. In fact, MEDTRONIC promoted to spine surgeons and patients the use of the product in dangerous off-label procedures, thereby demonstrating a conscious disregard for the health and safety of spinal fusion patients such as the Plaintiff.

13. Moreover, the actual rate of incidence of serious side effects from off-label use of Infuse® is, in fact, much greater than that disclosed by MEDTRONIC to spine surgeons and patients. With respect to the off-label approaches, MEDTRONIC failed to accurately disclose the significant off-label risks of which it knew or should have known.

14. Because of MEDTRONIC's wrongful conduct in actively and illegally promoting the off-label uses of Infuse®, and because of MEDTRONIC's additional wrongful conduct in minimizing, concealing, and/or downplaying the true risks of these non-FDA approved off-label uses of its product Infuse®, thousands of spine patients, including Plaintiff, underwent surgeries without knowing the true risks inherent in the off-label use of Infuse®.

15. These patients and their physicians relied on MEDTRONIC's false and misleading statements of material fact including statements and publications by MEDTRONIC's "opinion leaders," "thought leaders" and sales representatives. MEDTRONIC orchestrated a marketing campaign from at least 2002 to the present to persuade spine surgeons to use Infuse® in dangerous off-label uses in the spine. Indeed, absent MEDTRONIC's extensive off-label promotion campaign, physicians, such as the Plaintiff's spine surgeon, would never have performed these especially risky off-label procedures.

16. As a result of the off-label use of Infuse® in her spinal surgery, Plaintiff LIGIA VANESSA CHAPETON suffered bodily injuries and damages as described herein.

PARTIES

17. At all times relevant herein, Plaintiffs LIGIA VANESSA CHAPETON and GARY SEYMOUR are individuals who are residents and citizens of New York, New York County.

18. At all times relevant herein, Defendant MEDTRONIC, INC. is a Minnesota corporation, with its principal place of business at 710 Medtronic Parkway, Minneapolis, Minnesota 55432.

19. At all times relevant herein, Defendant MEDTRONIC SOFAMOR DANEK USA, INC. is a Tennessee corporation, with its principal place of business at 2600 Sofamor Danek Drive, Memphis, Tennessee 38132.

20. At all times relevant herein, Defendant ROGER HARTL, M.D. ("Dr. HARTL"), an adult individual, is a resident and citizen of New York with a principle place of business at Weill Cornell Medical College 525 East 68th Street STARR-651 - Box 99 New York, New York County, NY 10065.

21. At all times relevant herein, Dr. HARTL was engaged in the practice of medicine, pursuing the specialty of neurosurgery, and was obliged to bring to bear during the practice of his profession the professional skills, knowledge and experience which he possessed and/or was

obliged to possess, and to pursue his profession in accordance with reasonably safe and acceptable standards of medicine, in general, and neurosurgery, in particular.

22. At all times herein mentioned, each of the Defendants were the agent, servant, partner, aider and abettor, co-conspirator and/or joint venturer of each of the other Defendants herein and was at all times operating and acting within the purpose and scope of said agency, service, employment, partnership, conspiracy and/or joint venture and rendered substantial assistance and encouragement to the other Defendants, knowing that their collective conduct would or reasonably could lead to harm Plaintiffs.

23. At all times herein mentioned, Defendants and each of them, were fully informed of the actions of their agents and employees, and thereafter no officer, director or managing agent partner of Defendants repudiated those actions, which failure to repudiate constituted adoption and approval of said actions and all Defendants and each of them, thereby ratified those actions.

24. Further, at all times material to the matters alleged in this Complaint, Defendants each acted as the agent of the other Defendants, within the course and scope of this agency relationship regarding the acts and omissions alleged. Together, these Defendants entered into an agreement to commit the acts alleged herein, and engaged in the course of conduct and in furtherance of those goals. These Defendants acted in concert, aided and abetted each other, conspired to engage in the common course of misconduct alleged herein for the purpose of enriching themselves at the expense of Plaintiffs.

25. There exists and, at all times herein mentioned, there existed a unity of interest in ownership between certain Defendants and other certain Defendants such that any individuality and separateness between the certain Defendants has ceased and these Defendants are the alter ego of the other certain Defendants and exerted control over those Defendants. Adherence to the fiction of the separate existence of these certain Defendants as entities distinct from other certain Defendants will permit an abuse of the corporate/limited liability partnership privilege, would sanction a fraud, and/or would promote injustice.

26. The harm which has been caused to Plaintiffs resulted from the conduct of one, or various combinations of the Defendants, through no fault of the Plaintiffs. There may be uncertainty as to which one or combination of Defendants caused the harm. Defendants have superior knowledge and information on the subject of which one or combination of Defendants caused Plaintiffs' injuries and damages.

JURISDICTION AND VENUE

27. Jurisdiction and venue are properly laid in this County, as all acts complained of occurred in New York County, and Defendant Dr. HARTL regularly practice medicine in New York County.

ALLEGATIONS

1) The Infuse® Combination Device and FDA Approval History

28. On July 2, 2002, the FDA granted Medtronic's premarket approval application (PMA) for the "InFUSE® Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device." Exhibit A, FDA PMA Approval Letter at 1. For the sake of brevity, Plaintiffs refer to this approved device as the Infuse® combination device.

29. The FDA's approved description of the combination device stated,

> The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device consists of two components containing three parts-a tapered metallic spinal fusion cage, a recombinant human bone morphogenetic protein and a carrier/scaffold for the bone morphogenetic protein and resulting bone.

Exhibit B, FDA Approved Label at 1.

30. The FDA also requires that both components of the Infuse® combination device are used together: "These components must be used as a system. The InFuse™ Bone Graft component must not be used without the LT-CAGE™ Lumbar Tapered Fusion Device component." *Id.*

31. The cage component maintains the spacing and temporarily stabilizes the diseased region of the spine, while the Infuse® bone graft component is used to form bone, which is intended to permanently stabilize (fuse) this portion of the spine.

32. The FDA identified rhBMP-2 as "the active ingredient in the InFUSE™ Bone Graft component." *Id.* at 2. As noted in the Introduction to this Complaint , Plaintiffs refer to the bio-engineered bone growth protein, rhBMP-2, as "Infuse®." During surgery, Infuse® is soaked onto and is intended to bind with the absorbable collagen sponge that is designed to resorb, or disappear, over time. As the sponge dissolves, Infuse® stimulates the cells to produce new bone.

33. Certain bone morphogenetic proteins ("BMP"s) have been studied for decades because of their ability to heal bone and potentially decrease or eliminate the need for bone graft harvesting from other parts of the body. Scientists isolated the gene for one protein (rhBMP-2) from bone tissue and used molecular biology techniques to create genetically engineered cells that produce large quantities of rhBMP-2.

34. Thus, Infuse® is an alternative or supplement to other grafting materials to help fuse vertebrae in the lower (lumbar) spine to treat degenerative disc disease. For years, autologous bone graft has been considered the "gold standard" in fusion surgery. In an autologous bone graft — or "autograft" — the surgeon procures bone graft material from another part of the patient's body, typically from the patient's pelvis or iliac crest, and implants the bone graft in the site where fusion is desired. Successful fusions occur at significantly high rates in autograft procedures, as the harvested bone exhibits all the properties necessary for bone growth. As an alternative to autograft, patients can undergo an "allograft" procedure. In an allograft procedure bone is taken from the cadavers of deceased people who have donated their bone to so called "bone banks." Bio-engineered and bio-manufactured bone-growth materials, including Infuse®, provide a newer option to both traditional bone graft procedures.

35. Attempting to seize on this potentially lucrative opportunity to develop a bio-engineered bone-growth protein, Sofamor Danek Group, Inc., a Memphis, Tennessee-based spinal device maker ("Sofamor Danek"), acquired the exclusive rights to rhBMP-2 for spinal applications in February 1995. In October 1996, Sofamor Danek filed with the FDA an application for an Investigational Device Exemption to conduct a pilot study on the effects of

rhBMP-2 in humans, marking the first step to obtaining approval to commercially market BMP. In January 1999, MEDTRONIC purchased Sofamor Danek for $3.6 billion.

36. When the FDA approved the Infuse® combination device in 2002, it did so for one specific spinal fusion procedure. According to the FDA's PMA approval, the Infuse® combination device can only be used in an Anterior Lumbar Interbody Fusion ("ALIF") procedure, involving a single-level fusion in the L4-S1 region of the lumbar spine. Ex. A, FDA PMA Approval Letter at 1; Ex. B, FDA Approved Label at 3. ALIF is performed by approaching the spine from the front of the body through an incision in the abdomen and is primarily used to treat pain resulting from degenerative disc disease.[1]

37. The use of Infuse® for posterior lumbar fusion surgery has never been approved by the FDA.[2] Likewise, the FDA has never approved the use of Infuse® in spinal fusion surgeries without an LT-CAGE™. Thus, the use of Infuse® in either manner consists of an off-label use.

38. Physicians may use FDA-approved medical devices in any way they see fit — either on-label or off-label, but, as explained in greater detail below, medical device companies are prohibited by federal law from promoting off-label uses for their medical devices. Such promotion to physicians or patients any off-label use of Infuse® constitutes misbranding.

39. During the FDA Advisory Committee Panel ("FDA Panel") hearing on January 10, 2002 concerning potential FDA approval of Infuse®, Panel members voiced concerns regarding potential off-label use of the product, and asked MEDTRONIC to describe its efforts to guard against off-label use of the product.

[1] While the product's label remains substantially the same as that approved by the FDA in 2002, the FDA has made minor amendments to the label through post-approval supplements. For example, on July 29, 2004, the FDA approved a supplement expanding the indicated spinal region from L4-S1 to L2-S1 and later granted approval for uses in certain oral maxillofacial surgeries.

[2] There are numerous other lumbar spine surgical procedures for which Infuse® was not approved, and for which it has never been approved, such as Posterior Lumbar Interbody Fusion ("PLIF"), Posterolateral Fusion and Transforaminal Lumbar Interbody Fusion ("TLIF"), and these uses of the Infuse® would also be considered off-label.

40. In response to FDA concerns of off-label applications, one MEDTRONIC consultant, who is alleged to have received hundreds of thousands of dollars in the form of kickbacks from consulting agreements promoting Infuse®, dismissed the FDA Panel's concerns of off-label use, stating: "this specific application before the panel today is through an anterior approach," and thus, "seems to me to be outside the scope of what we ought to be focusing on today."

41. Reiterating its concerns on off-label use, the FDA Panel cautioned MEDTRONIC to guard against procedures outside the specifically approved ALIF procedure provided in the labeled application. The FDA Panel's admonishment included concerns voiced by Panel member Dr. John Kirkpatrick that off- label use could result in harm to patients. More specifically, the use of the ***tapered*** LT-Cage™ — which is difficult to implant in a posterior approach—would, if required, "prevent a majority of surgeons from applying this from a Posterior Lumbar Interbody Fusion [PLIF] perspective." In other words, the FDA explicitly warned MEDTRONIC against promoting Infuse® for use in off- label PLIF procedures because, according to the statements of the FDA Panel, such use could endanger patients.

2) <u>The Medical Device Amendments</u>

a) <u>Premarket Approval</u>

42. The Medical Device Amendments of 1976 ("MDA") to the FDCA established the current regulatory framework for medical device approval.

The MDA contains a three-class classification system for medical devices. Class I devices pose the lowest risk to consumers' health, do not require FDA approval for marketing, and include devices such as tongue depressors. Class II devices pose intermediate risk and often include special controls including post-market surveillance and guidance documents. Finally, Class III devices pose the greatest risk of death or complications and include most implantable surgical devices such as cardiac pacemakers, coronary artery stents, automated external defibrillators, and several types of implantable orthopedic devices for spine and hip surgery. Infuse® is a Class III device.

43. Manufacturers such as MEDTRONIC seeking to market Class III devices, such as Infuse®, are required to submit a Premarket Approval Application ("PMA") that must be evaluated and approved by the FDA. The PMA requires the manufacturer to demonstrate the product's safety and efficacy to the FDA through a process that analyzes clinical and other data, including: (1) technical data and information on the product, including non-clinical laboratory studies and clinical investigations; (2) non-clinical laboratory studies that provide information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests of the device—all of which must be conducted in compliance with federal regulations which set forth, *inter alia*, criteria for researcher qualifications, facility standards and testing procedures; and (3) clinical investigations in which study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations are provided, including the results of any investigation conducted under an Investigational Device Exemption ("IDE").

i) **The Food And Drug Administration (FDA) Applications Are Limited By The Applicants' Claimed "*Intended Use*"**

44. The PMA is based on the manufacturer disclosing all of the pertinent information about the medical device for the FDA to review. One of the most significant parts of the premarket application is the medical device's claimed "*intended use*" as these are the only uses that are evaluated by the FDA in their premarket approval process for efficacy and safety.[3] The Code of Federal Regulations (CFR), Title 21, Chapter I, Subchapter H-Medical Devices, § 801.4 (2012) (Meaning of intended uses.), defines "intended use" in terms of "objective intent" of the manufacturer in a medical device approval setting:

> The words intended uses or words of similar import . . . refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions

[3] 21 U.S.C.§ 360e(c)(2)(A)(iv) (2012).

> or may be shown by the circumstances surrounding the distribution of the article. **This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives**. It may be shown by the circumstances that the article is, **with the knowledge** of such persons or their representatives, offered **and used for a purpose for which it is neither labeled nor advertised**. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer...But **if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses** to which the article is to be put.[4] (emphasis added).

45. The FDCA requires Class III medical devices to be demonstrated to be safe and effective for each *intended use*.[5]

46. The FDA ensures that medical devices intended for use in humans are demonstrated by the manufacturer to be safe and effective for each of their *intended uses* and that the labeling of such medical devices bore true and accurate information concerning their intended use.

47. The FDA determines what is on label on the basis of a product's "intended use."

48. The "intended use" of a medical device is defined at 21 C.F.R. § 801.4 (2012) as "the objective intent of the persons legally responsible for the labeling of devices..." "The intended use or uses of a medical drug or device may also be determined from advertisements, promotional material, oral statements by the product's manufacturer or its representatives, and any other relevant source."[6] Manufacturers must obtain FDA approval for each intended use.

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[4] 21 C.F.R. § 801.4 (2012) ("Meaning of 'Intended Uses" Under the "General Labeling Provisions" for the "Labeling" section.) (emphasis added).
[5] *See* 21 U.S.C. §§ 321, 355, 360c (2012).
[6] 65 Fed. Reg. § 14286 (Mar. 16, 2000). There is also a definition of "intended use" for prescription drugs that is essentially the same as the definition for medical devices; *see* 21 C.F.R. § 201.128 (2012).

ii) **The Premarket Application Process Includes Not Only The Medical Device Itself But Also The Product Labeling**

49. Not only is the medical device itself part of the premarket application process, but the labeling and packaging that comes with it. Each premarket submission must also include all proposed "labeling" for the medical device and *its intended use*.

50. The FDCA requires that a submission for approval of a device include proposed labeling for the proposed *intended uses* of the medical device that includes, among other things, the conditions for therapeutic use.

51. In order to be approved by the FDA, an applicant for premarket approval of a Class III medical device must demonstrate its safety and effectiveness for "the persons for whose use the device is represented or intended" and "with respect to the conditions of use prescribed, recommended, or suggested in the label..."[7]

52. The FDA performs a risk-benefit assessment of the medical device and then determines the adequacy of the manufacturer's proposed label. When the FDA approves a premarket application, the FDA finds that based on the information supplied by the manufacturer, a device is safe and effective under the specific and limited conditions of use included on the label and that the label is not false or misleading.[8]

53. A manufacturer is required to give adequate directions for the use of a medical device such that a "layman can use a device safely and for the purposes for which it is intended"[9], and conform to section 801.15 requirements governing the appearance of the label.

54. Premarket approval of the product is conditioned upon the applicant incorporating any labeling changes as directed by the FDA, which typically includes labeling the product's risks and benefits, as well as adequate directions for use.[10] "Labeling" encompasses all written, printed or graphic material accompanying the drug or device[11], and therefore broadly

[7] 21 U.S.C. § 360c(a)(2)(A)-(B) (2012).
[8] 21 U.S.C. § 360e(d)(1)(A), (d)(2) (2012).
[9] 21 C.F.R. § 801.5 (2012).
[10] *See, e.g.*, 21 U.S.C. § 352 (2012).
[11] *Id.* §§ 321(k), (m) (2012).

encompasses nearly every form of promotional activity, including not only "package inserts" but also advertising.[12]

iii) **The FDA, By Its Regulations and PMA Process, Restricts Manufacturers From Promoting "Off-Label" Non-Intended Uses**

55. When the FDA approves a medical device, the agency approves the device for the specific intended use set out in the product's approved labeling. A use approved by the FDA is usually referred to as an "approved", "labeled" or "intended use". A use that does not appear in the labeling is not approved as safe and effective as it never went through the FDA's premarket approval review. It is known as an "unapproved," "off-label," or "new use." For the sake of consistency, in this complaint, Plaintiffs refer to such unapproved uses as "off-label" or "unintended" uses.

56. A medical device manufacturer is not permitted to promote and/or market a new medical device submitted to the FDA under the premarket approval process until it had an approval for its intended use, including approval for the proposed labeling. Moreover, if approved, the medical device manufacturer is permitted to promote the medical device only for the medical conditions or *indicated uses* specified in the approved labeling. Therefore, a medical device manufacturer is not permitted to promote a medical device in an "off-label" manner, since the FDA did not approve the medical device for that medical condition or use.

57. A central feature of the FDCA is that it prohibits medical device companies from promoting their devices for "off-label" uses.[13]

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[12] *See, e.g.*, 21 C.F.R. § 202.1 (2012).

[13] Congress created a very limited "safe harbor" for certain "off-label" promotion between 1997 and 2006. The "safe harbor" allowed manufacturers to provide copies of peer reviewed scientific articles to physicians. See 21 U.S.C. §§ 360aaa, 360aaa-1 (2012) (these statutes had a sunset clause of September 30, 2006 and were never renewed, see 21 C.F.R. §§ 99.101 (2012) (current FDA regulations on this issue)). As further discussed herein, Plaintiffs, however, allege that Medtronic's "off-label" promotional efforts far exceeded these "safe harbor" activities (*i.e.* redistribution of peer reviewed articles) and included other impermissible acts, including but not limited to, using paid consultants, key opinion leaders, seminars, presentations, in-house corporate paid doctors operating phone banks to instruct outside surgeons over the phone when they call Medtronic headquarters on how to perform "off label" procedures, as well as drafting,

58. "[O]ne of the [FDCA's] core objectives is to ensure that any product regulated by the FDA is 'safe' and 'effective' for its intended use."[14]

59. A medical device that is promoted for non-intended "off-label" uses is deemed "misbranded" in violation of 21 U.S.C. § 352(f) (2012) (misbranding).

60. Under the FDCA and its accompanying regulations, a medical device manufacturer must include all intended uses in the label; otherwise the medical device is misbranded.[15]

61. A product is "misbranded" when the directions and indications for the unapproved uses that the manufacturer "intends" the product to be used for have not been included on the label.[16]

62. The FDCA's accompanying regulations require that medical devices sold by manufacturers have adequate directions for use[17], and failure to have adequate instructions for sue is considered "misbranding,"[18] which is prohibited.[19]

63. The FDCA requires medical device manufacturers to disclose all material facts in advertising and labeling[20], and false or misleading labeling is considered "misbranded"[21], which is prohibited.[22]

64. The distribution of a "misbranded" medical device is prohibited pursuant to 21 U.S.C. §§ 331(a), (k) (2012) and 21 U.S.C. § 352(f) (2012).

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editing and ghostwriting the so-called "peer reviewed articles" while paying the listed "authors" (who are acting as agents for the company) millions of dollars without disclosing these efforts or payments within the contents of the articles or anywhere publically, all to actively and consciously over promote the "off-label" uses of Infuse®.

[14] *United States v. Caronia*, 703 F3d 149, 166 (2nd Cir. 2012) quoting *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133, (2000).

[15] 21 C.F.R. § 801.4 (2012).

[16] 21 C.F.R. § 801.4 (2012).

[17] 21 C.F.R. § 801.5 (2012).

[18] 21 U.S.C. § 352 (f) (2012).

[19] 21 U.S.C. § 331(b).

[20] 21 U.S.C. § 321 (n) (2012).

[21] 21 U.S.C. § 352 (a).(q)(1) (2012).

[22] 21 U.S.C. § 331(b).

65. The FDCA provides that a medical device is misbranded if, among other things, the labeling did not contain adequate directions for use.[23] Adequate directions for use could not be written for medical indications or uses for which the medical device has not been approved, and accordingly, directions for "off-label" use cannot be included in the approved labeling.

66. "Similarly, a medical device that is distributed for a 'new use' is 'adulterated,' see 21 U.S.C. 351(f), and 'misbranded,' see 21 U.S.C. 352(f). An adulterated or misbranded product is prohibited from distribution in interstate commerce (21 U.S.C. 331(a), (k))..."[24] The reason a medical device that is distributed for an unapproved new use is considered 'misbranded' is that the device fails to include adequate directions and warnings.

67. "Off-label" use of a medical device is a use that was not approved by the FDA, including different applications or surgical approaches, different dosages, different patient populations, or different conditions from those stated in the label.

68. The FDA prohibits medical device manufacturers from promoting any "off-label" uses through advertisement, recommendations, or suggestions (*See* 21 C.F.R. § 202.1(e)(4)(i)(a) (2012) for the provision that advertising "shall not recommend or suggest any use that is not in the labeling.")

69. A manufacturer is prohibited from promoting a use of the product that is not the specified use in the PMA or the label.[25]

70. A manufacturer who wishes to modify the labeling, packaging, design, or indications for use of its device has to comply with a supplemental PMA process.[26]

71. The FDA strictly regulates manufacturers based on the intended use of the device, and manufacturers cannot deviate from those specifications without permission. If a

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[23] 21 U.S.C. § 352(f)(1) (2012); *See also* 21 C.F.R. § 801.5 (2012).
[24] Fed. Reg. § 14286 (Mar. 16, 2000).
[25] 21 U.S.C. § 331(a) (effective 2013); *see also* 21 C.F.R. § 814.80 (2012) (providing that a "device may not be... advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order to the device.")
[26] 21 C.F.R. § 814.39(a) (2012).

manufacturer wants to change the intended use for a device, it must follow the FDA's established procedure.[27]

72. Federal law requires a manufacturer to ensure that any warranty statements it voluntary makes are truthful, accurate, not misleading, and consistent with applicable federal and state law.[28]

73. Under the FDCA and its accompanying regulations, a medical device manufacturer must include all intended uses in the label otherwise the device is misbranded.[29]

74. Under the FDCA, medical device manufacturers are prohibited from introducing the adulteration or misbranding of any medical device into interstate commerce.[30]

75. A Class III device that fails to meet and/or comply with the requirements of the PMA is considered to be adulterated under Section 501(f) of the FDCA and cannot be marketed. A device may also be adulterated or misbranded because it lacks requisite FDA clearance or approval.[31] Furthermore, "[l]isting of unapproved uses in the... advertising... results in an adulterated medical device."[32] Marketing the device for an unapproved intended use thus makes the device both misbranded and adulterated.

76. The FDCA prohibits the introduction into interstate commerce of any medical device that is misbranded[33], and also prohibits the alteration of any part of the labeling,

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[27] *See* 21 C.F.R. § 814.39(a) (2012) (specifying how a manufacturer can add new indications for use through the supplemental PMA process); 21 U.S.C. § 360e(d)(6) (2012).
[28] 21 U.S.C. § 331(b) (effective 2013). It should be noted that the FDA approval letter for Infuse® specifically states that the FDA "...does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws." *See* http://www.accessdata.fda.gov/cdrh_docs/pdf/P000058a.pdf (also attached hereto as Exhibit "A").
[29] 21 C.F.R. § 801.4 (2012).
[30] 21 U.S.C. § 331(b) (effective 2013).
[31] FDCA §§ 501(f), 502(o), 21 U.S.C. §§ 351(f), 352(o).
[32] 59 Fed. Reg. 59821 (Nov. 18, 1994).
[33] 21 U.S.C. § 331(a) (effective 2013).

advertising, or promotional material for a medical device while the device is held for sale after shipment in interstate commerce that results in the device being misbranded.[34]

77. A medical device manufacturer may not tell the FDA that its device should or will be used only in certain procedures, and then actively encourage physicians to use the device in other procedures. By promoting and/or advertising the medical device to physicians for a new unapproved use the medical device manufacturer has shown that the intended use of the device has changed. Off-label promotion violates federal law, the PMA and may carry criminal penalties.[35]

iv) The FDA, By Its Regulations And PMA Process, Restricts Manufacturers From Distributing Products For "Off-Label" Non-Intended Uses

78. The FDA "generally prohibits the manufacturer... from distributing a product... for any intended use that the FDA has not approved as safe and effective..."[36]

79. "If a manufacturer knows, or has knowledge of facts that would give him notice that a device... is to be used for conditions, purposes, or uses other than the ones for which he offers it, the manufacturer is required to provide adequate labeling for such other uses."[37]

80. FDA regulations prohibit a manufacturer from "express[ing]" an "intent" or merely "know[ing]" or having "notice" that its product "is to be used" "off-label".[38]

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[34] 21 U.S.C. § 331(k) (effective 2013).
[35] *See* 21 U.S.C. § 333(a) (2012). This conduct also violates State parallel common laws. The Second Circuit held that "off-label promotion that is false or misleading is not entitled to First Amendment protection." *United States v. Caronia*, 703 F.3d 149, 160-69 (2d Cir. 2012). Further, the Ninth Circuit has assumed that "off-label" promotion violates federal law. *Carson v. Deput Spine, Inc.*, 365 Fed. App'x 812, 815 (9th Cir. 2010).
[36] 65 Fed. Reg. § 14286 (Mar. 16, 2000).
[37] 21 C.F.R. § 801.4 (2012). An example of direct knowledge would be when the manufacturer has a sales representative in the operating room. An example of notice would be when the manufacturer has a majority of sales for non-intended off-label uses.
[38] 21 C.F.R. §§ 201.100, 201.128 (2012); *see* 21 U.S.C. § 352(f)(1) (2012).

81. Thus, a manufacturer that knows a device is being used for "off-label" uses is required to notify the FDA and obtain approval for labeling modifications consistent with the alternate use. Failure to do so renders the device adulterated and misbranded.

82. The FDCA prohibits the introduction, or delivery for introduction, into interstate commerce of any device that is adulterated or misbranded.[39]

83. FDA regulations also prohibit a manufacturer from "express[ing]" an "intent" or merely "know[ing]" or having "notice" that its product "is to be used" "off-label".[40] Any manufacturer's statement, whether true or not-and even mere knowledge of use-can create a new "intended use," and thus a misbranded or adulterated product.

84. The FDA regulations make it plain that it does not regulate the practice of medicine. However the FDA regulations have also made it crystal clear that this is wholly separate and apart from the restrictions the FDA has placed on a manufacturer for promoting or distributing an unapproved product.

> Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient... **Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.**[41]

85. Therefore, although the FDA does not regulate the practice of medicine,[42] the FDCA does prohibit a manufacturer from promoting a use of the product that is not the specified approved use.[43]

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[39] 21 U.S.C. § 331(b) (2012).

[40] *See* 21 C.F.R. §§ 201.100, 201.128; *see also* 21 U.S.C. § 352(f)(1). Medtronic routinely had Corporate Sales Representatives directly in the operating room during "off-label" surgeries. These Corporate Sales Representatives had direct knowledge of the "off-label" use of Infuse®, which is imputed to Medtronic. As further discussed herein, Medtronic's sales of Infuse® were over 85-90% "off-label". This staggering high statistic is sufficient evidence to not only put Medtronic on notice of the "off-label" use, but it also highlights how successful Medtronic was with its illegal over promotional campaign for "off-label" uses. *See Minneapolis Firefighters*, 278 F.R.D. at 456 discussed further herein.

[41] 21 U.S.C. § 397 (emphasis added).

[42] 21 U.S.C. § 396.

[43] 21 U.S.C. § 331(a) (effective 2013); *see also* 21 C.F.R. § 814.80 (2012) (providing that a

86. Should a manufacturer wish to market a device "for a new or different indication for use, the premarket notification submission must include appropriate supporting data to show that the manufacturer has considered what consequences and effects the change, modification, or new use might have on the safety and effectiveness of the device."[44]

v) **FDA Regulations And PMA Requires A Manufacturer To File A Supplemental Application For "Off-Label" Uses**

87. In addition to limiting premarket approval to only those devices demonstrated to be safe **and** effective, the actual stated purpose of premarket approval is "[t]o ensure the disapproval of PMA's for devices that have not been shown to be safe **and** effective or that do not otherwise meet the statutory criteria for approval."[45]

88. This prohibition in the FDCA is intended to protect patients and consumers by ensuring that manufacturers do not promote devices that are unsafe or ineffective based on the FDA's standards and review.

89. The terms of 21 C.F.R. § 801.4 render any device "adulterated" or "misbranded" when the manufacturer knew or should have known ("knowledge of facts that would give him notice") that the doctor/hospital/etc. to which the device was sold was going to use it in an "off-label" manner.

90. Under 21 C.F.R. § 801.4, the FDA regulations state that "if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put."

91. Consequently, federal law requires that a medical device manufacturer, who has knowledge or even notice of "off-label" use, is required to provide adequate labeling.

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device "may not be ... advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device.")

[44] 21 C.F.R. § 807.87(g) (2012).

[45] 21 C.F.R. § 814.2 (2012).

92. The manufacturer must seek "adequate labeling for such a device which accords with such uses to which the article is to be put."

93. If such a device does not have the required "adequate labeling" the medical device is "adulterated" and "misbranded."

94. "Off-label" use is not approved by the FDA as "safe and effective," which approval is a prerequisite to placing any material on the labeling concerning any use. A manufacturer must seek a PMA supplement for the new, unapproved, "off-label" use.

95. 21 C.F.R. § 814. 39(a) (2012) requires a manufacturer to file a PMA Supplement for changes that affect the safety or effectiveness of a device. This section expressly requires that a manufacturer file a PMA for any "new indications for use of the device." This is not a permissive choice, but rather a federally mandated requirement, as shown by the use of the term "**shall**" in the federal regulation.

96. After FDA's approval of a PMA, an applicant **shall** submit a PMA supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA ... While the burden for determining whether a supplement is required is primarily on the PMA holder, **changes for which an applicant shall submit a PMA supplement include, but are not limited to, the following types of changes if they affect the safety or effectiveness of the device**:

(1) **New indications for use of the device**

(2) **Labeling changes**...[46]

97. A manufacturer must submit a PMA Supplement to the FDA for review/approval of changes affecting safety and effectiveness of a device (specifically including new indications)[47]; when a manufacturer desires to market or distribute a device "for a new or different indication for use, the premarket notification must include appropriate data to show the

[46] *See* 21 C.F.R. § 814.39(a) (2012) "PMA Supplements" (emphasis added).
[47] 21 U.S.C. § 814.39(a) (2012).

manufacturer has considered what consequences and effects the change, modification, or new use might have on the safety and effectiveness of the device."[48]

98. If a manufacturer wishes to obtain approval for a new or different intended use, the manufacturer must go through a lengthy and expensive process to obtain FDA approval for the new use, either by filing a PMA Supplement application pursuant to § 814.39, or by filing a new PMA application.

99. Any changes the manufacturer believes could affect the safety and effectiveness of the device, including any intention to promote the device for new, unlabeled uses, must be submitted, via a "PMA Supplement," to the FDA for approval. "After FDA's approval of the PMA, an applicant shall submit a PMA supplement for review and approval by FDA before making a change affecting the safety and effectiveness of the device for which the applicant has an approved PMA... While the burden for determining whether a supplement is required is primarily on the PMA holder, changes for which an applicant shall submit a PMA supplement include, but are not limited to, the following types of changes if they affect the safety or effectiveness of the device: (1) *New indications for use of the device*..."[49]

vi) <u>The FDA, By Its Regulations and PMA Process, Prohibits Misleading Or False Promotion And Marketing Activities</u>

100. Under the FDCA and FDA's implementing regulations, labeling, promotional advertisements, and making claims about medical devices are deemed misleading if they fail to disclose certain information about the product's risks.[50]

101. Generally, to comply with the FDCA and FDA's implementing regulations, and therefore the PMA, such promotional pieces:

a. Cannot be false or misleading in any particular;[51] and

[48] 21 C.F.R. § 807.87(g) (2012).
[49] 21 C.F.R. § 814.39(a) (2012) (emphasis added).
[50] Infuse® was initially approved as a combination medical product which contained a device (the LT-Cage) and a collagen sponge made up of BMP-2 (a Drug). The FDA classified this combination product as a medical device. Medtronic often sold the collagen sponge (drug) separately from the LT-Cage (the device).

b. Must reveal material facts about the product being promoted, including facts about the consequences that can result from use of the product as suggested in the promotional piece;[52]

c. Must be about only approved intended uses.[53]

102. The FDA regulates the manufacture, sale, and distribution of medical devices in the United States under the authority of the FDCA. This authority includes oversight of labeling and advertising for all medical devices.[54]

103. A medical device shall be deemed to be misbranded if its labeling is false or misleading in any particular.[55] Labeling or advertising may be considered misleading if it fails to reveal material facts about the product being promoted, including facts about the consequences that can result from use of the product as suggested in a promotional piece.[56]

104. "In the case of any restricted device distributed for sale in any State, if (1) its advertising is false or misleading in any particular, or (2) it is sold, distributed, or used in violation of regulations prescribed under section 520(e)."[57]

105. Advertisements for restricted devices must include "a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications..."[58]

106. Restricted device advertisements must not be false or misleading[59] and must reveal facts that are material about the product being advertised, including facts about the consequences that can result from use of the product as suggested in an ad.[60]

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[51] Drugs and devices are misbranded under the Act if their labeling is false or misleading in any particular. 21 U.S.C. § 352(a) (2012).
[52] 21 U.S.C. § 321(n) (2012); 21 C.F.R. §§ 1.21, 202.1(e)(5)(iii) (2012).
[53] 21 C.F.R. § 801.4 (2012).
[54] *See* 21 U.S.C. § 352(a), (n), (q), & (r) (2012).
[55] 21 U.S.C. § 352(a) (2012).
[56] *See* 21 U.S.C. § 321(n) (2012).
[57] 21 C.F.R. § 502 (q) (2012).
[58] *See* 21 U.S.C. § 352(r)(2) (2012).
[59] 21 U.S.C. § 352(q)(1) (2012).

vii) **After A Medical Device Is Approved, The Manufacturer Still Has Requirements, Including General Reporting Requirements To The FDA, Mandated By FDA Regulations And PMA Approval Process**

107. A Medical device manufacturer's obligations do not end with Premarket Approval.

108. Even after premarket approval issues, manufacturers are required to report to the FDA "no later than 30 calendar days after the day: the manufacturer receive[s] or otherwise become[s] aware of information, from any source, that reasonably suggests that a device" marketed by the manufacturer:

a. May have caused or contributed to death or serious injury; or

b. Has malfunctioned and this device or a similar device [likewise marketed by the manufacturer] would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.[61]

109. In addition, manufacturers are required to make periodic reports to the FDA regarding approved devices, such reports to include summaries of:

a. Unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices and known to or that reasonably should be known to the applicant.

b. Reports in the scientific literature concerning the device and known to or that reasonably should be known to the applicant.[62]

110. Once the FDA has approved a medical device through the PMA application process (such as Infuse®), the manufacturer/applicant is required to comply with the standards set forth in the PMA approval letter. "A device may not be manufactured, packaged, stored, labeled,

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[60] 21 U.S.C. § 321(n) (2012).
[61] 21 C.F.R. § 803.50(a); *see also* 21 U.S.C. § 360i(a) (further detailing the post approval reporting requirements applicable to device manufacturer).
[62] 21 C.F.R. § 814.84(b)(2).

distributed, or advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device."[63]

111. Under federal law, a medical device manufacturer has a continuing duty to monitor the product after premarket approval and to discover and report to the FDA any complaints about the product's performance and any adverse health consequences of which it became aware and that are or may be attributable to the product.

112. Following approval, a medical device manufacturer is required to report adverse events associated with the use of the product, *i.e.* those that may have caused serious injury or death or has malfunctioned and would likely cause or contribute to death or serious injury if recurred.[64]

113. The medical device manufacturer is required to report any incidents or information that reasonably suggests that the device (1) "[m]ay have caused or contributed to a death or serious injury" or (2) "[h]as malfunctioned" in a manner that would likely "cause or contribute to a death or serious injury" if it recurred.[65]

114. Another general reporting requirement for Class III medical devices after PMA approval is that the manufacturer is obligated to inform the FDA of new clinical investigations or scientific studies concerning the device about which the manufacturer knows or reasonably should know.[66]

115. Further, the FDCA subjects approved devices to reporting requirements.[67] For example, the manufacturer must update the FDA when it learns of investigations or scientific studies concerning its device[68], or incidents where the device used in any manner "[m]ay have caused or contributed to a death or serious injury," either due to malfunction or normal

[63] 21 C.F.R. § 814.80 (2012).
[64] 21 C.F.R. § 803.50(a) (2012); 21 U.S.C. § 360i(a) (2012).
[65] 21 C.F.R. § 803.50(a) (2012); 21 U.S.C. § 360i(a) (2012).
[66] 21 C.F.R. § 814.84(b)(2) (2012).
[67] 21 U.S.C. § 360i (2012).
[68] 21 C.F.R. § 814.84(b)(2) (2012).

operation.[69] The FDA can revoke its approval based on these post-approval reports.[70] The manufacturer must establish internal procedures for reviewing complaints and event reports.[71]

116. Medical device manufacturers are required by federal regulation to "establish and maintain" an adverse event database.[72]

viii) Post Approval, The FDA, By Its Regulations And PMA Process, Requires A Manufacturer To Follow Good Manufacturing Practices

117. Under 21 C.F.R. § 820.1(a) (2012) of the Quality System (QS) Regulation for Medical Devices, current good manufacturing practice (CGMP) requirements are set forth in this quality system regulation. The requirements in this part govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. The requirements in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (FDCA). This part establishes basic requirements applicable to manufacturers of finished medical devices.

118. 21 C.F.R. § 820.5 (2012) "Quality Systems", the FDA regulations state, "Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part."

119. 21 C.F.R. § 820.30 (2012) "Design controls" state (i) *Design changes*. Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.

120. 21 C.F.R. § 820.3(z)(2) (2012) *Design validation* means establishing by objective evidence that device specifications conform with user needs and intended use(s).

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[69] *Id.* § 803.50(a) (2012).
[70] 21 U.S.C. §§ 360e(e)(1), 360h(e) (2012).
[71] 21 C.F.R. § 820.198(a) (2012).
[72] *See* 21 C.F.R. § 803.1(a) (2012).

121. 21 C.F.R. § 820.22 (2012): "Quality Audit" states: "Each manufacturer shall establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system."

122. 21 C.F.R. § 820.160(a) (2012): "Distribution" states: Each manufacturer shall establish and maintain procedures for control and distribution of finished devices to ensure that only those devices approved for release are distributed and that purchase orders are reviewed to ensure that ambiguities and errors are resolved before devices are released for distribution.

123. 21 C.F.R. § 820.170(a) (2012): "Installation" states: Each manufacturer of a device requiring installation shall establish and maintain adequate installation and inspection instructions, and where appropriate test procedures. Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation. The manufacturer shall distribute the instructions and procedures with the device or otherwise make them available to the person(s) installing the device.

124. 21 C.F.R. § 803 (2012), states: Manufacturers must include information that is reasonably known to the manufacturer, timely make Medical Device Reporting ("MDR") submissions, define the procedures for implementing corrective and preventative actions, and review sampling methods for adequacy of their intended use.

125. 21 C.F.R. § 820.100 (2012) "Corrective and Preventive Action" states: (a) [e]ach manufacturer shall establish and maintain procedures for implementing corrective and preventive action.

126. The procedures shall include requirements for:

a. Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;

b. Investigating the cause of nonconformities relating to product, processes, and the quality system;

c. Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;

d. Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device; and

e. Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.

b) MEDTRONIC's Conduct in Violation of the FDCA

127. MEDTRONIC violated these FDCA statutes and accompanying regulations by falsely and misleadingly promoting Infuse® for off-label uses, misbranding Infuse®, failing to report to the FDA adverse events, and failing to submit a supplemental approval to account for the new intended use and design of Infuse® .

128. MEDTRONIC's violation of these FDCA statutes and accompany regulations, as discussed above, constitutes violation of the state law tort causes of action alleged in this Complaint, as set forth herein.

129. MEDTRONIC's violation of the FDCA statutes and accompanying regulations, as discussed above, directly caused or significantly contributed to the off-label use of Infuse® generally, and directly caused or significantly contributed to the off-label use of Infuse® in this particular Plaintiff, and MEDTRONIC's misconduct in this regard thus caused or contributed to Plaintiff's injuries and damages.

3) MEDTRONIC's Campaign of Off-Label Promotion of Infuse®

a) Generally

130. In spite of the very specific and limited FDA approval of Infuse®, MEDTRONIC has successfully (and profitably) increased off-label sales of Infuse® through "consulting" and royalty agreements with physicians and off-label promotion efforts by its sales representatives. MEDTRONIC paid outside physician "Opinion Leaders" handsome sums in return for

publishing studies and medical journal articles which downplayed and concealed the risks of adverse events from off-label use while actively promoting off-label use of Infuse®, delivering presentations explaining, endorsing, and promoting off-label applications of the product, and directly advocating off-label uses of Infuse® to other spine surgeons, while minimizing the risks or dangers to patients from these uses.

131. Medical device companies, including MEDTRONIC, look for surgeons who are known as "Opinion Leaders" and who will not only use a high volume of their products, but who can and will persuade other surgeons to use a particular device. Opinion leaders are physicians whose opinions on medical procedures and medical devices are held in high regard by other surgeons. If these influential physicians are willing to promote the use of a certain device, then other surgeons are likely to follow suit and use that device, sometimes including off-label uses which are illegal for the company itself to promote.

132. Prior to the date of Plaintiff's spine surgery which involved off-label Infuse®, MEDTRONIC provided millions of dollars in sometimes undisclosed payments to certain spine surgeon Opinion Leaders who published articles in medical journals, delivered presentations at continuing medical education courses, and appeared at consulting engagements to promote off-label applications of Infuse® in the spine. "Medtronic paid a total of approximately $210 million to physician authors of Medtronic-sponsored studies from November 1996 through December 2010 for consulting, royalty, and other miscellaneous arrangements." *Staff Report on Medtronic's Influence on Infuse Clinical Studies*, U.S. Senate Committee on Finance, October 25, 2012. MEDTRONIC, while providing spine surgeons with MEDTRONIC-funded studies and published articles purporting to support the efficacy and safety of the off-label uses, simultaneously and systematically concealed or downplayed other non-MEDTRONIC-funded studies and articles demonstrating serious and frequent adverse events caused by the same off-label uses.

133. MEDTRONIC's sales force directed physicians to Opinion Leaders, as well as their written work (paid for by MEDTRONIC) to further drive off-label sales of Infuse®. Certain

sales representatives went so far as to recommend dosages of Infuse® in risky off-label procedures, and guide surgeons through off-label uses of the product during surgery.

134. In this way, and as described in greater detail below, MEDTRONIC consciously and deliberately orchestrated a campaign to end-run the FDA's 2002 approval of and labeling for the Infuse® device. Indeed, even after a settlement with the Department of Justice as a result of this very activity, MEDTRONIC continued its practice of providing lucrative consulting fees (amounting to millions of dollars per year) to surgeons who actively promoted off-label use of Infuse®, often with direct involvement by MEDTRONIC's senior management.

135. The federal judiciary has recognized a genuine risk that financial conflicts of interest induce bias in scientific research. The Federal Judicial Center's key reference guide for judges considering scientific issues in their cases explains, "Judges and juries . . . must consider financial conflicts of interest when assessing scientific testimony. The threshold for pursing the possibility of bias must be low." Reference Manual on Scientific Evidence (Third) Preface (2011). In addition, research published in the *New England Journal of Medicine*, as well as other surveys, show that information brought by industry representatives to physicians impacts medical decision-making. Thus, the comprehensive off-label, unsubstantiated and otherwise misleading marketing of Infuse® to physicians, including Plaintiff's surgeon, guided by MEDTRONIC's goal of expanding the market for Infuse® beyond FDA-approved uses, exposed patients, including Plaintiff, to an increased risk of bone overgrowth, radiculitis and other complications from their spinal fusion surgeries.

b) Opinion Leader Dr. Thomas A. Zdeblick

136. Thomas A. Zdeblick, M.D., the Chairman of the Department of Orthopedics and Rehabilitation at the University of Wisconsin, received substantial sums from MEDTRONIC; he was paid over $19 million from MEDTRONIC from 2003 to 2007 for consulting services and royalty payments. Although Dr. Zdeblick only disclosed annual payments exceeding $20,000 in University conflict of interest forms, he actually received between $2.6 and $4.6 million per year. In 2007 alone, Dr. Zdeblick received $2,641,000 in consulting fees from MEDTRONIC.

From 1998 through 2004, Dr. Zdeblick was paid an annual salary of $400,000 by MEDTRONIC under a contract that only required him to work eight days per year at a MEDTRONIC site in Memphis, Tennessee, and to participate in "workshops" for surgeons.

137. Dr. Zdeblick has been a significant contributor to MEDTRONIC's promotion of Infuse®, authoring seven peer-reviewed articles on rhBMP-2 and appearing as a presenter at medical conferences and symposia in which the topics included discussion of off-label uses of the product. On a MEDTRONIC-owned website, "www.Back.com," Dr. Zdeblick describes the advantages of Infuse® and appears in an online video discussing the benefits of the product.

138. As discussed more fully *supra*, on January 16, 2009, *The Wall Street Journal* reported on a letter sent by Senator Charles Grassley to Kevin P. Reilly, President at the University of Wisconsin, regarding Defendants' consulting and royalty payments to Dr. Zdeblick, who co-authored preliminary studies that led to the FDA's approval of Infuse®. Although the University is required to monitor its researchers' financial conflicts-of-interest, the amounts MEDTRONIC paid Dr. Zdeblick far exceeded those he reported to the University. Specifically, Dr. Zdeblick was required to disclose annual amounts in excess of $20,000 per year, and in one year reported payments in excess of $40,000. In reality, Dr. Zdeblick received between $2.6 million and $4.6 million per year from MEDTRONIC, totaling an astonishing $19 million in payments, from 2003 through 2007.

139. As revealed in a June 20, 2009 article in the *Milwaukee Journal Sentinel*, Dr. Paul A. Anderson, an orthopedic surgeon and colleague of Dr. Zdeblick at the University of Wisconsin School of Medicine and Public Health, was paid $150,000 by MEDTRONIC for just eight days of work. Dr. Anderson, along with MEDTRONIC consultants Drs. Boden, Keith H. Bridwell, and Jeffrey C. Wang, authored a July 2007 article in *Journal of Bone and Joint Surgery* article, titled "What's New in Spine Surgery." The article discussed, among other things, a study that examined the use of Infuse® in an off- label Posterolateral Fusion procedure. According to the authors, the study reported that Infuse® improved fusion rates when used in combination with iliac crest bone graft in a procedure in which the BMP was wrapped around

local bone as a bulking agent. According to the authors, the study's findings suggested that "the current [Infuse®] kit, while likely not sufficient as a stand-alone graft substitute for the posterolateral spine, can provide a significant enhancer effect, improving the success of an autogenous bone graft."

140. On June 20, 2009, the *Milwaukee Journal Sentinel* reported that, during calendar year 2008, MEDTRONIC paid Dr. Zdeblick $2 million in royalty payments for eight days of consulting work, and that Dr. Paul Anderson received $150,000 in MEDTRONIC consulting fees for working just eight days.

c) Norton Hospital Leatherman Spine Center Opinion Leaders

141. Another set of highly compensated surgeons, those affiliated with the Norton Hospital Leatherman Spine Center in Louisville, Kentucky, collectively received more than one million dollars in consulting fees in 2006 alone, including Drs. John R. Johnson ($162,750), Steven D. Glassman ($200,300), Rolando M. Puno ($106,000), John R. Dimar, II ($192,300), David Rouben ($109,300), Mitch Campbell ($212,000) and Mladen Djurasovic ($55,900). These same MEDTRONIC-funded surgeons have written extensively on off-label uses of Infuse®. These surgeons have collectively authored at least 15 articles addressing the use of bone morphogenetic proteins (BMPs), including many of the early medical articles on the use of Infuse® in off-label posterolateral lumbar and anterior cervical fusion procedures.

142. A confidential witness in a qui tam action, described in greater detail below, specifically Confidential Witness 1 ("CW1"), has testified that several surgeons from the Leatherman Spine Center were requested by MEDTRONIC to speak at MEDTRONIC-sponsored physician talks attended by between ten and twenty-five surgeons, including several "pretty high profile" physicians. At these physician talks, a MEDTRONIC consultant, such as one of the surgeons at the Leatherman Spine Center, provided presentations covering the purported benefits of off-label usage of Infuse®. According to CW 1, "What [MEDTRONIC] would do is bring in one of their 'paid consultants' and set up a dinner in the area and invited a number of physicians to attend." The guest surgeon—the "paid consultant"— would then

"basically give a presentation on off-label usage." Importantly, these physician talks were also attended by all MEDTRONIC sales representatives who worked in the area.

d) Opinion Leader Dr. Jeffrey Wang, M.D.

143. Another prominent MEDTRONIC consultant, Jeffrey Wang, M.D., the Chief of Spine Surgery for the Department of Orthopaedic Surgery and Executive Co-Director of the University of California, Los Angeles's ("UCLA") Comprehensive Spine Center, also spoke about off-label uses of Infuse®. Dr. Wang received $275,000 in royalty and consulting payments from MEDTRONIC from 2003 until 2008.

144. Furthermore, Dr. Wang failed to disclose his substantial financial relationship with MEDTRONIC while researching MEDTRONIC products, which violated UCLA's policy requiring him to do so. For example, on a disclosure form to UCLA dated January 10, 2007, Dr. Wang checked "no" when asked if he received income of $500 or more from MEDTRONIC, notwithstanding the fact that MEDTRONIC was, at that very moment, funding one of Dr. Wang's studies. In fact, Dr. Wang received $14,600 on January 4, 2007 for "lecture and teachings at spine meetings and universities in Korea for one week." As a result of his repeated failures to disclose payments received from MEDTRONIC, Dr. Wang lost his position as Executive Co-Director of UCLA's Comprehensive Spine Center.

e) Walter Reed "Opinion Leaders:" Timothy Kuklo, M.D. and David Polly, M.D.

145. Former Chief of Orthopaedic Surgery at Walter Reed Army Medical Center ("Walter Reed") Dr. Timothy Kuklo was another of MEDTRONIC's highly compensated "consultants." During his eight years of consulting for MEDTRONIC, Dr. Kuklo was handsomely rewarded for downplaying concerns of adverse events caused by Infuse®, promoting unreasonably dangerous off-label uses to his fellow surgeons, and publishing falsified medical research in peer-reviewed medical journals. Dr. Kuklo received over $800,000 in fees from 2001 to 2009 for consulting, speaking, travel, and training services, the vast majority of which was in the years following the DOJ settlement.

146. On September 28, 2006, Dr. Kuklo baldly misrepresented the seriousness of adverse effects associated with the off-label use of Infuse® in the cervical spine when he appeared as a "distinguished guest surgeon" at a MEDTRONIC Spine Division Business Overview Conference Call. He, alongside fellow MEDTRONIC consultant Dr. Rick Sasso, who received $150,000 in consulting fees in 2006, responded to concerns raised by a Merrill Lynch analyst, who asked about "issues that have come up in the past in terms of potential side effects with using Infuse® in the cervical region." Both doctors dismissed these concerns, attributing the problems exclusively to dosage error and concealing the true cause.

147. In August 2008, Dr. Kuklo published a study in *The Journal of Bone and Joint Surgery* comparing clinical outcomes of tibial fracture patients requiring fusions. The article reported sixty-seven (67) patients received a traditional autogenous bone graft, while sixty-two (62) were treated with Infuse® (some of which were off-label uses), and claimed the Infuse® group had "strikingly" better outcomes than patients receiving the autogenous bone graft. Specifically, the autograft group had successful fusions in 76% of procedures, while the union rate for the Infuse® group was significantly better at 92%.

148. Dr. Kuklo claimed patients who received Infuse® experienced favorable outcomes in other clinical measures as well. Specifically, the study concluded that "the primary outcome measures of union, rate of infection, and reoperation were all improved with rhBMP-2," and that those treated with Infuse® had a "strikingly lower infection rate (3.2%), which we believe is directly attributable to rhBMP-2."

149. On May 13, 2009, *The New York Times* reported that the U.S. Army had concluded an investigation into Dr. Kuklo's study touting the benefits of Infuse® to treat wounded soldiers injured in Iraq and concluded he had falsified the entire study. Col. J. Edwin Atwood, the physician who led the Army's inquiry, described it as "the ultimate tragedy and catastrophe in academic medicine."

150. The true facts regarding Dr. Kuklo's study were only uncovered when one of the study's supposed "co-authors," Lt. Col. Romney C. Andersen, was congratulated on its

publication by a colleague. After this discovery, Lt. Col. Andersen alerted Army investigators who found that:

a. Dr. Kuklo listed four other Army surgeons as "co-authors" without their knowledge, and none of whom participated in or reviewed the article's preparation or submission for publication;

b. The signatures of the four physicians listed as co-authors on the copyright release forms submitted to *The Journal of Bone and Joint Surgery* were forged by Dr. Kuklo;

c. Contrary to Army policy, Dr. Kuklo did not obtain publication review or clearance from Walter Reed prior to submitting the article for publication; and

d. The published results of the article suggested a much higher efficacy rate for Infuse® than is supported by the experience of the purported co- authors.

e. The number of cases cited by Dr. Kuklo in the article differed from the number of cases contained in the U.S. Army's wartime casualty database, with no explanation for the discrepancies in the article. Indeed, according to one of the Army's investigators, Col. Norvell V. Coots, the study cited higher numbers of patients and injuries than the hospital could account for having as patients. According to Col. Coots, "It's like a ghost population that were reported in the article as having been treated that we have no record of ever having existed … this really was all falsified information."

151. *The Journal of Bone and Joint Surgery*, after receiving correspondence from Walter Reed dated November 6, 2008 disclosing the findings of their investigation, formally retracted the article and banned Dr. Kuklo from submitting further papers to the journal.

152. MEDTRONIC continued to pay Dr. Kuklo as a consultant even after his article was discovered to be largely fabricated and thus retracted by *The Journal of Bone and Joint Surgery*. Indeed, MEDTRONIC only placed Dr. Kuklo on "inactive status" after the story was published in *The New York Times*. By this time, Dr. Kuklo had given countless presentations on behalf of MEDTRONIC about off-label use of the product.

153. As noted in a May 19, 2009 follow-up article in *The New York Times*, when questioned about its ties to Dr. Kuklo, MEDTRONIC repeatedly declined to disclose when it began its financial relationship with him or the extent of funding it provided. MEDTRONIC also failed to disclose its relationship with Dr. Kuklo to Senator Grassley during his inquiry.

154. Another highly compensated MEDTRONIC consultant involved in the promotion of off-label Infuse® use, Dr. David Polly, a professor and Chief of the Spine Service at the University of Minnesota Department of Orthopaedic Surgery, received consulting fees from MEDTRONIC totaling $1.14 million from 2003 to 2007. As with Dr. Kuklo, Dr. Polly was not mentioned in MEDTRONIC's disclosure list to Senator Grassley, and as with Dr. Kuklo, MEDTRONIC's financial relationship with Dr. Polly began while the surgeon was on active military duty at Walter Reed.

155. Although Dr. Polly has claimed that his consulting relationship with MEDTRONIC did not begin until 2004, documents obtained through requests under the Freedom of Information Act ("FOIA") reveal that MEDTRONIC paid almost $30,000 in travel expenses for Dr. Polly to speak at various medical conferences in the Bahamas, San Diego, and a $10,000 trip to Switzerland, while he was stationed at Walter Reed in 2003. Dr. Polly attended these conferences to report on his research that purportedly demonstrated that Infuse® was more cost effective than traditional spinal fusion procedures.

156. According to an article co-authored by Drs. Polly and Kuklo published in the November 2004 issue of "Minnesota Medicine," rhBMP-2 was used in more than 100 military patients with traumatic bone fractures who had served in Iraq and Afghanistan. Although the use of Infuse® in tibial fractures was not approved until April 30, 2004, Dr. Polly reported that the "decision to use rhBMP-2 was made early in the Afghanistan conflict and was based on evidence from clinical trials in Europe on open tibial fractures that suggested use of rhBMP-2 not only improved bone healing but led to a decreased number of secondary interventions and lower rates of infection." According to Dr. Polly, "the military's experience with rhBMP-2 has been favorable."

157. MEDTRONIC reimbursed Dr. Kuklo for a meeting with MEDTRONIC representatives in Memphis, Tennessee on April 20, 2004 regarding "Review of BMP Trauma and Spine Surgery" prior to the November 2004 article being published.

158. In May 2006, Dr. Polly, seeking a government grant for a similar research into the use of Infuse® and antibiotics to treat traumatic and infected bone fractures, testified before the Defense Subcommittee of the U.S. Senate Appropriations. Dr. Polly stated that he was "speaking on behalf of the American Academy of Orthopedic Surgeons." However, according to information recently released by Senators Grassley and Baucus, Dr. Polly actually billed MEDTRONIC $7,000 in connection with his Senate testimony. Therefore, Dr. Polly was speaking on behalf of MEDTRONIC, not the American Academy of Orthopedic Surgeons, as he had claimed. Furthermore, Dr. Polly billed MEDTRONIC a total of $50,000 over several months for his lobbying efforts in securing the $466,644 Department of Defense grant for this Infuse® research study. Additionally, from July 2005 to September 2007, Dr. Polly repeatedly billed MEDTRONIC for his frequent meetings, telephone calls, and email correspondence with numerous MEDTRONIC senior executives, billing reports which MEDTRONIC approved.

f) Other Various Opinion Leaders

159. Several physicians who authored a May 2003 article describing positive results of Infuse® used in the cervical spine were paid tens of thousands of dollars in consulting fees by MEDTRONIC. The article, "New Technologies in Anterior Cervical Spine Fixation," published on SpineUniverse, a website intended for the general public that provides information regarding spinal disorders and treatment, described the physicians' use of Infuse® "in the cervical spine with very good results." According to the authors, "[p]reliminary results are promising and Infuse® may be especially appropriate in people undergoing multiple level fusions" (emphasis added)—i.e., for indications outside FDA limited approval to single-level fusion procedures.

160. One of the authors of this article, Dr. Regis Haid, Jr., received consulting fees of $50,000 from MEDTRONIC in 2006 and similar amounts in the previous two years. Another author, Dr. Gerald Rodts, received payments of $80,000 from MEDTRONIC in 2006 and similar

amounts in the previous two years. The SpineUniverse article does not mention that its authors received compensation from MEDTRONIC, nor do the website profiles of Dr. Haid and Dr. Rodts, both of whom serve on the publication's editorial board, disclose their financial ties to MEDTRONIC.

161. Dr. Haid was also the lead author of an article describing the results of the study of Infuse® in off-label PLIF procedures that was halted in December 1999 after several patients experienced adverse incidents of uncontrolled bony overgrowth. In addition, two of the article's other authors—Dr. J. Kenneth Burkus and Dr. Charles L. Branch—received consulting fees from MEDTRONIC. Specifically, MEDTRONIC paid Dr. Branch $154,900 in 2006 and similar amounts in the preceding two years, while Dr. Kenneth Burkus—who has written over a dozen articles addressing the use of rhBMP-2, including studies examining the use of Infuse® in off-label PLIF and anterior cervical procedures—received $416,775 in 2006 and similar amounts in the two preceding years.

162. CW 1 stated that Drs. Lawrence "Larry" G. Lenke and Keith H. Bridwell, two surgeons from Washington University in St. Louis – where Dr. Kuklo worked as an associate professor until recently – similarly acted as "Opinion Leaders" or "guest surgeons" during "corporate visits" in which MEDTRONIC would invite targeted surgeons to attend training sessions in Memphis, Tennessee. While in Memphis, the visiting surgeons met with MEDTRONIC corporate officers, product managers, and guest surgeons, such as Drs. Lenke and Bridwell. The visiting surgeons also received "hands-on training" on Infuse®, including instruction in cadaver labs. According to CW1, who personally attended two such meetings, "[t]here was training on off- label procedures, for sure." The visiting surgeons "would bring up the use of Infuse® and ask how to use it, and [the guest surgeons] would show them how to do it." CW1 stated that MEDTRONIC chose which surgeons to invite to these corporate visits based, in part, upon the volume of Infuse® procedures they performed.

4) The Design Defect in Infuse®

163. Despite the fact that the FDA only approved Infuse® for use in the spine in combination with use of the LT-CAGE™, MEDTRONIC has designed and sold Infuse® separately from the LT-CAGE™.

164. By designing Infuse® for sale without the LT-CAGE™ and promoting and selling it as such, MEDTRONIC has unlawfully designed, manufactured, marketed and sold a new device for which the FDA never weighed the risk versus the benefit and never approved.

165. Moreover, this new device presents risks and dangers that render it defective.

166. MEDTRONIC was required, but failed, to apply for supplemental pre-market approval from the FDA due to changes in the design specifications and components of the Infuse® combination device.

167. As a result, the Infuse® implanted in Plaintiff LIGIA VANESSA CHAPETON without the LT-CAGE™ did not perform as safely as an ordinary consumer would have expected it to perform when used or misused in an intended or reasonably foreseeable way, based on the FDA's approval, and the benefits of the design did not outweigh the risks of that design.

168. On information and belief, MEDTRONIC sells the Infuse® component separately from the LT-CAGE™ in order to illegally and improperly promote dangerous off-label uses of Infuse®. MEDTRONIC does not disclose in its promotional or marketing campaign that Infuse® was approved for only one method of use in the lumbar spine. As a result of concealing the approval, the FDA Panel's admonitions not to use it in a posterior approach because of the additional dangers and risks posed, and downplaying the adverse events associated with its use in this off-label manner by its Opinion Leaders in methods described, MEDTRONIC significantly increased the sale of the Product and reaped the benefits of its concealment and campaign of deceit.

169. Infuse® has become a best seller for MEDTRONIC. Sales of Infuse® were approximately $800 million for the 2011 fiscal year and the vast majority of these sales were

attributable to off-label use of the product. Off-label promotion results in off-label uses of Infuse®, which account for 85% to 90% of all spine surgeries involving Infuse®.

5) Medtronic's Fraud and Misrepresentations as to Infuse®

170. MEDTRONIC systematically manipulated the medical literature regarding Infuse® to misrepresent the product's safety and efficacy and to conceal its financial ties to the studies' authors and its role in writing the articles. From at least 2002 until *The Spine Journal* articles were published in the Summer of 2011, MEDTRONIC engaged in a ghostwriting program of the articles and study reports in order to suppress any information about the real risks and dangers posed by off-label posterior use of Infuse®. The specific misrepresentations regarding the products' safety and efficacy, described in greater detail below, include (1) the concealment of adverse events, (2) the omission of related risks, including but not limited to dangerous bone overgrowth, and an over-emphasis on the problems posed by traditional bone graft procedures, such as autograft; (3) inadequate or no information about the dose response of patients, such that doctors were misled as to how much Bone protein to use and what amount of bone growth would result.

a) Fraudulent, Ghost-Written 2004 Spine Journal Article by Dr. Haid, Dr. Burkus, Dr. Branch and Dr. Alexander

171. One example of MEDTRONIC's misrepresentations regarding the safety and efficacy of off-label uses of Infuse® is found in a 2004 article published in *The Spine Journal*: Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages, authored by Regis W. Haid, MD, Charles L. Branch, Jr., MD, Joseph T. Alexander, MD, J. Kenneth Burkus, MD. The Spine Journal 4 (2004) 527-539.

172. This study revealed statistically significant variables concerning the radiographic presence of bone in the spinal canal and foramina in the group that received Infuse®. However, the authors denied that intraspinal bone formation had any clinical implications. *Id.* at 528. By denying that the bone had clinical implications, the doctors and MEDTRONIC were concealing the real risk and danger posed by use of Infuse® in this manner.

173. MEDTRONIC employees, including employees of its Marketing Department, were involved in ghost-writing this 2004 *Spine Journal* article, as well as peer-review correspondence in defense of the article prior to its publication. Ex. C, Senate Finance Committee Report at 15-17. MEDTRONIC employees edited the draft manuscript for the article to include comments supportive of the use of Infuse® in an off-label posterior approach. These edits were ultimately included in the published article. In addition, MEDTRONIC employees covertly participated in the peer-review process by drafting at least part of a letter on behalf of Dr. Burkus and the other physician authors named on the paper, responding to peer-reviewer criticism and allegations of bias. The response letter never disclosed MEDTRONIC's direct role in editing the article or the fact of MEDTRONIC's payments to each of the physician authors. In particular, by the end of 2003, Dr. Haid, Dr. Burkus and Dr. Alexander received $7,793,000, $722,000 and $826,655 respectively from MEDTRONIC. *Id.* at 5, 17. Dr. Haid, Dr. Burkus and Dr. Alexander received these funds to create research, leading to publications and presentations, that would promote the use of Infuse®, in particular off-label uses of the product.

b) Fraudulent, Ghost-Written 2005 *Journal of Bone and Joint Surgery (JBJS)* Article by Dr. Burkus, et al.

174. Indeed, MEDTRONIC employees were substantively involved in producing eleven journal articles authored by the company's paid physician consultants, including several that specifically addressed the off-label use of Infuse® in posterior approach surgeries. Ex. C, Senate Finance Committee Report, at 6-7. In addition to the instance of ghost-writing in the 2004 *Spine Journal* article described above, a MEDTRONIC employee, Dr. Julie Bearcroft, directed the omission of a complete accounting of adverse event data regarding the use of Infuse® from a 2005 *Journal of Bone and Joint Surgery (JBJS)* article by Burkus, et al. *Id.* at 9 (describing Bearcroft's "significant changes" to Dr. Burkus's article, including changes in content, and the omission of a table of adverse events in the published paper, following her email correspondence recommending omission of "significant detail" concerning adverse event data).

c) Medtronic's Employees and Agents, including its Opinion Leaders, Repeated their Fraudulent and Misleading Statements in Presentations and Discussions with Physicians Nationwide

175. Plaintiffs are informed and believe that the misrepresentations and intentional omissions of risks and adverse effects that are described above have also been made at presentations and conferences where the off-label uses of Infuse® in spinal surgeries have been promoted by physicians hired by MEDTRONIC to make presentations to other doctors at medical meetings and conferences. These presentations were intended by MEDTRONIC to be cloaked in proper science and appear to be presentations about reputable science and research, when, in fact, as described they were tailored and ghostwritten by the Company in order to hide the truth about Infuse® and push the sales of Infuse®. These physicians either wittingly or not became pawns of MEDTRONIC in hawking the sale of this Product in a manner unapproved by the FDA.

176. Following the limited FDA approval of Infuse® in 2002, Medtronic published a "Fact Sheet". The Fact Sheet represented, in part, the following:

> **Fact Sheet**
>
> ***INFUSE® Bone Graft/LT-CAGE®*** Lumbar Tapered Fusion Device... Spinal fusion surgery with INFUSE® Bone Graft and the LT-CAGE® Device **is essentially the same as traditional autograft procedures**, without the need for the additional surgery to harvest bone from the patient's hip. **Scientists determined** that rhBMP-2, with an absorbable collagen sponge as the carrier, (INFUSE® Bone Graft) **is an effective replacement for autograft bone in spinal fusion surgery**. This conclusion is **based on data resulting from a large-scale, multi-center, prospective, randomized, two-year study** involving 279 degenerative disc disease patients implanted with INFUSE® Bone Graft and the LT-CAGE® Lumbar Tapered Fusion Device. The **study assessed the safety, efficacy** and therapeutic benefits of the new procedure as compared to traditional autograft procedures... The data showed that the study met all of its primary endpoints... Long-term cost offsets (within two years of surgery): **Significantly fewer complications** that would require follow-up visits...[73]

[73] Medtronic, Fact Sheet (2002) *available at* *http://www.medtronic.com/downloadablefiles/InFuse - InFuse Therapy Fact Sheet.pdf*

177. In the "Fact Sheet" Medtronic made representations that Infuse® is essentially the same autograft procedures. Medtronic stated that "Scientists determined..." without mentioning the fact that these "scientists" were extremely highly compensated by Medtronic to the tune of millions and in some cases, tens of millions of dollars.

178. In the "Fact Sheet" Medtronic states that "The **study assessed the safety, efficacy** and therapeutic benefits of the new procedure as compared to traditional autograft procedures... The data showed that the study met all of its primary endpoints... Long-term cost offsets (within two years of surgery): **Significantly fewer complication**s that would require follow-up visits...[74]".

179. However, nowhere does Medtronic state that Medtronic employees significantly altered the printed/reported results of those "studies" to reflect better outcomes for Infuse® and worse outcomes for the alternative procedures, than what was actually observed.

180. In the Fact Sheet, Medtronic did not simply provide the studies, but rather Medtronic wrote opinions and summaries of the studies for their own promotional purposes.[75]

181. As alleged in detail herein these "scientific studies" were knowingly false and misleading. Medtronic manipulated the scientific data as well as the so-called peer reviewed literature that was written by Medtronic's secret agents who were compensated hundreds of

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[74] *Id.*

[75] Congress created a very limited "safe harbor" for certain "off-label" promotion between 1997 and 2006. The "safe harbor" allowed manufacturers to provide copies of peer reviewed scientific articles to physicians. See 21 U.S.C. § 360aaa, 360aaa-1 (these statutes had a sunset clause of September 30, 2006 and were never renewed, see 21 C.F.R. §§ 99.101 (current FDA regulations on this issue). As further discussed herein, Plaintiffs, however, allege that Medtronic's "off-label" promotional efforts far exceeded these "safe harbor" activities (i.e. redistribution of peer reviewed articles) and included other impermissible acts, including but not limited to, using paid consultants, key opinion leaders, seminars, presentations, as well as drafting, editing and ghost writing the so-called "peer reviewed articles" while paying the listed "authors" (who are acting as agents for the company) millions of dollars without disclosing these efforts or payments within the contents of the articles or anywhere publically, all to actively and consciously over promote the "off-label" uses of Infuse®.

millions of dollars. Medtronic went so far as to improperly ghost write and edit these studies and literature before publication.

182. The falsity of Medtronic's representations contained in the Fact Sheet has been independently confirmed to be false by the Medtronic funded YODA study as discussed in detail further herein.

d) The Widespread Repudiation of Medtronic-Funded Studies that Touted the Safety and Efficacy of Infuse®

183. MEDTRONIC's misrepresentations in the 2004 *Spine Journal* article and 2005 *Journal of Bone and Joint Surgery (JBJS)* article concerning the risks associated with Infuse® are part of a larger pattern of fraudulent concealment by Medtronic concerning adverse events related to use of the product in spinal surgeries. MEDTRONIC's fraudulent statements regarding the safety and efficacy of Infuse® have been rejected by these and other subsequent medical studies, as discussed below.

i) June 2011 Special Edition of *The Spine Journal*

184. The June 2011 edition of *The Spine Journal* published a series of articles describing MEDTRONIC's failure to report accurately the side effects from its clinical trials, the statements by authors, paid by MEDTRONIC, downplaying the risks associated with Infuse® and over-emphasizing problems associated with traditional non-Infuse® bone graft products used in spine fusion procedures, and MEDTRONIC's failure to report that many of the authors who studied and promoted Infuse® had significant financial ties to MEDTRONIC with a median range of $12 to $16 million per study. The industry-sponsored articles omitted mention of indications from the earliest trials of inflammatory reactions, adverse back and leg pain events, radiculitis, retrograde ejaculation, urinary retention, bone resorption, and implant displacement. They also omitted mention of sterility and cancer risks associated with rhBMP-2, as reported in FDA documents and hearings.

185. An analysis led by Dr. Eugene Carragee at Stanford University, and published in the June 2011 edition of *The Spine Journal*, identified thirteen Infuse® studies sponsored by

MEDTRONIC which reported no adverse events associated with the product. Eugene J. Carragee, Eric L. Hurwitz & Bradley K. Weiner, *A Critical Review Of Recombinant Human Bone Morphogenetic Protein-2 Trials In Spinal Surgery: Emerging Safety Concerns And Lessons Learned*, the Spine Journal 11, 471-491 (2011). The analysis by Dr. Carragee and his team includes a table that identifies each of the thirteen articles and quotes the authors' comments regarding Infuse® -related observed adverse events in study patients. *Id.* at Table 1, "Original industry-sponsored rhBMP-2 clinical studies and reported adverse event rates because of rhBMP-2."

Table 1
Original industry-sponsored rhBMP-2 clinical studies and reported adverse event rates because of rhBMP-2

Authors	rhBMP-2 Placement	rhBMP-2, n	rhBMP-2 Adverse events (%)	Authors comment regarding rhBMP-2–related observed adverse events in study patients
Boden et al. [2]	Anterior interbody (LT-cage, lumbar, rhBMP-2)	11	0	"There were no adverse events related to the rhBMP-2 treatment"
Boden et al. [3]	Posterolateral (lumbar, ± instrumentation)	20	0	"There were no adverse effects directly related to the rhBMP-2..."
Burkus et al. [5]	Anterior interbody (LT-cage, lumbar, INFUSE)	143[a]	0	"There were no unanticipated device-related adverse events..."
Burkus et al. [6]	Anterior interbody (bone dowel, lumbar, INFUSE)	[24][a]	0	"There were no unanticipated adverse events related to the use of INFUSE Bone Graft." (2002)
Burkus et al. [39]		79	0	None reported (2005)
Burkus et al. [40]	Anterior interbody (LT-cage, lumbar, INFUSE)	277	0	None reported
Baskin et al. [7]	Anterior interbody (cervical, INFUSE)	18	0	"There were no device-related adverse events"
Haid et al. [8]	Posterior interbody fusion (lumbar, INFUSE)	34	0	"No unanticipated device-related adverse events occurred"
Boakye et al. [41]	Anterior interbody (cervical, INFUSE)	24	0	"Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy.... a 100% fusion rate and nonsignificant morbidity"
Dimar et al. (2009)	Posterolateral (lumbar, INFUSE, pedicle screws)	53	0	None reported
Glassman et al. [42]	Posterolateral (lumbar, AMPLIFY, and pedicle screws)	[148][b]	0	None reported
Dimar et al. [10]	Posterolateral (lumbar, AMPLIFY, and pedicle screws)	239	0	"No adverse event that was specifically attributed to the use of rhBMP-2 matrix in the study group was identified"
Dawson et al. [11]	Posterolateral (lumbar, INFUSE, and pedicle screws)	25	0	None reported
Total	All types	780	0	99% CI <0.5% adverse event rate

rhBMP-2, recombinant human bone morphogenetic protein-2; CI, confidence interval.
[a] Report patients as in Burkus 2003, not included in total rhBMP-2 calculation.
[b] Possible subgroup of Dimar et al., 2009, not included in total rhBMP-2 calculation.
[c] These patient reported again in Burkus 2005.

186. Dr. Carragee's analysis further explained the falsity of these representations. He observed:

> Given that 780 patients received rhBMP-2 in these industry sponsored publications and that not a single adverse event had been reported, the estimated risk of rhBMP-2 use could be calculated to be less than 0.5% with 99% certainty. That is, the reported risk of an adverse event with rhBMP 2, based on the

> industry-sponsored data, was less than one-fortieth the risk of a course of commonly used anti-inflammatory or antibiotic medications.

Id. at 472.

187. Dr. Carragee's team, however, reviewed FDA documents and subsequent publications and found originally unpublished adverse events and internal inconsistencies. *Id.* at 471. Based on this review, Dr. Carragee suggested an estimate of adverse events associated with Infuse® in spinal fusion surgeries ranging from 10 percent to 50 percent depending on approach. *Id.*

ii) **June 2013 Yale Study Confirms Lack of Scientific Integrity of Medtronic-Sponsored Studies of Infuse®**

188. Following the unprecedented findings by *The Spine Journal*, Medtronic under its new CEO, Omar Ishrak commissioned a subsequent review of the effectiveness of Infuse®.

189. In August 2011, Medtronic provided a $2.5 million grant to Harlan Krumholz, M.D. to create the Yale University Open Data Access Project (YODA).[76] YODA's stated goal was to "increase transparency and enhance the public trust in industry-funded clinical trials by facilitating the independent assessment and dissemination of data relevant to the benefits and harms of drugs and devices."[77] Through YODA, Yale led independent and systematic reviews of the entire body of scientific evidence regarding the safety and effectiveness of Medtronic's recombinant bone morphogenetic protein-2 (rhBMP-2) product.

190. In a public response to the initiation of the YODA study, twenty-one (21) preeminent surgeons voiced their concern in the article A biologic without guidelines: the YODA project and the future of bone morphogenetic protient-2 research, published in The Spine Journal in October 2012. The surgeons provided in part:

> [a]s a specialty, **it is painful to consider how early prudent reporting of even the most obvious and suspicious adverse events might well have prevented a decade of serious complications** related to the use of rhBMP-2. In retrospect, we

[76] Center for Outcomes Research & Evaluation (CORE), YODA Project, *available at* http://medicine.yale.edu/core/projects/yodap/index.aspx.
[77] *Id.*

> can see how false confidence in a reportedly perfect safety profile promoted a period of BMP-2 application in areas of greater and greater potential danger. . . And yet, given the legacy of questionable research and limitations in the primary body of rhBMP-2 data, there is a possibility that expectations of YODA have been exaggerated.[78]

191. The article further noted that "clinical researchers cannot act as financially engaged business associates, and dispassionate investigators cannot be both credible authors and entrepreneurs in research involving human subjects...[m]any principal investigators in the Medtronic-sponsored trials had financial conflicts of unprecedented magnitude, the effect of which will be difficult to estimate, but nearly impossible to overestimate, in post hoc analyses."[79]

192. Even Dr. Krumholz, the creator of YODA, expressed his concerns stating, "This sounds eerily familiar to many of the transgressions we've read about from the pharmaceutical industry...It paints a picture of a company very heavily involved in the science; marketing contaminating the science; and the medical profession and researchers being complicit."[80]

193. In hopes to quell concerns of further impropriety, two academic teams, Oregon Health and Science University and University of York, conducted an independent review, on behalf of YODA, with full access to all of Medtronic's clinical trials, post-marketing and safety data regarding rhBMP-2.[81]

194. Oregon Health and Science University stated that "[t]he primary aims of this report are 1) to estimate the effectiveness and harms of rhBMP-2 in spinal fusion in a systematic review using the individual patent data (IPD) when available, and 2) to assess reporting biases in published articles of industry-sponsored studies."[82]

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[78] Carragee EJ, *A biologic without guidelines: the YODA project and the future of bone morphogenetic protein-2 research,* 12 Spine J. 878, 877-80 (2012).
[79] *Id.* at 878-79
[80] John Fauber, *Medtronic Helped Write, Edit Positive 'Infuse' Spine Studies*, (Oct 25, 2012), *available at* http://www.medpagetoday.com/PainManagement/BackPain/35551.
[81] rhBMP-2 Project, Center for Outcomes Research & Evaluation (CORE), YODA Project, *available at* http://medicine.yale.edu/core/projects/yodap/rhbmp/overview.aspx.
[82] Rongwei Fu et al., *Effectiveness and Harms of Recombinant Human Bone Morphogenic Protein-2 (rhBMP-2) in Spine Fusion: A Systematic Review and Meta-analysis, Executive Summary*, Oregon Health & Science University, 1 (2013), *available at*

195. Oregon Health and Science University released their findings in June of 2013 and found that "there was serious selective reporting and underreporting of adverse events in the published articles for both rhBMP-2 and ICBG groups, especially in the Medtronic trials published early. The actual rates of adverse events were much higher than reported."[83]

196. More specifically the Oregon Health and Science University reported that the IPD data contained "315 adverse events in the rhBMP-2 group and 274 adverse events in the autograft group two years after surgery."[84] These finding are in direct contrast with the Medtronic-sponsored studies, which simply reported either "no unanticipated device-related adverse events" or "no adverse events directly or attributable to rhBMP-2."[85]

197. Dr. Rongwei Fu, the lead author of the Oregon Health and Science University study, stated **"[w]e found a lot of reporting bias** in [Medtronic's] published papers that tends to overstate the benefits and played down the risks." Further, Dr. Fu said "**it was difficult to identify "clear indications" for using the product,** as Infuse® offered no additional benefits beyond the normal benefits of the spine surgery." [86]

198. Following an independent review of Medtronic's data, Oregon Health and Science University study found that Infuse® had more adverse events and an increased risk associated with its use, when compared to the gold standard traditional ICBG. Specifically, Infuse® resulted in:

a. a risk of cancer almost double that of ICBG;

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http://medicine.yale.edu/core/projects/yodap/rhbmp/463_158786_OHSU rhBMP-2 Final Report.pdf.

[83] *Id.* at 9.

[84] *Id.*

[85] Eugene J. Carragee, Alexander J. Ghanayem, Bradley K. Weiner, *A challenge to integrity in spine publications: years of living dangerously with the promotion of bone growth factors,* 11 Spine J. 480, 482-83, 463-468 (2011).

[86] Christopher Weaver, *Studies Fail to Back Medtronic Spine Product*, The Wall Street Journal, (June 17, 2013), *available at* http://online.wsj.com/article/SB10001424127887323836504578551801689098558.html.

b. retrograde ejaculation was 4.76 times more likely with Infuse® than with ICBG;

c. spinal instability was 2.79 times more likely to occur as a vertebral fracture in patients using Infuse® as opposed to ICBG;

d. heterotopic bone growth was 5.57 times more likely to occur in PLIF and TLIF spinal fusions using Infuse® as opposed to ICBG;

e. osteolysis or bone destruction was 4.26 times more likely to occur in a TLIF and 3.17 times more likely in a PLF using Infuse® than a spinal fusion using ICBG; and

f. hardware failure was as high as 8.37 times more likely to occur using Infuse® than with ICBG.[87]

199. Furthermore, a meta-analysis of the IPD showed that "there was moderate strength of evidence of **no consistent differences between rh-BMP-2 and ICBG in overall success of fusion**."[88] (Emphasis added).

200. This finding directly contradicts the false and misleading marketing materials provided by Medtronic directly to physicians and consumers on their websites which touted a greater fusion rates with Infuse® when compared to ICBG.

201. Similarly, University of York stated that the three objectives of their independent review of Medtronic's data were to "1) [e]xamine the potential benefits of rhBMP-2; 2) Examine the potential harms of rhBMP-2; and 3) Assess the reliability of the published evidence base."[89]

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[87] Rongwei Fu et al., *Effectiveness and Harms of Recombinant Human Bone Morphogenic Protein-2 (rhBMP-2) in Spine Fusion: A Systematic Review and Meta-analysis, Executive Summary*, Oregon Health & Science University, 5 (2013), *available at* http://medicine.yale.edu/core/projects/yodap/rhbmp/463_158786_OHSU rhBMP-2 Final Report.pdf.

[88] *Id.* at 5.

[89] Jennifer V.E. Brown et al., Systemic review and meta-analysis of the safety and efficacy of recombinant human bone morphogenic protein-2 (rhBMP-2) for spinal fusion, Centre for Reviews and Dissemination University of York, 3 (2013), *available at* http://medicine.yale.edu/core/projects/yodap/rhbmp/463_158787_York rhBMP-2 Final Report.pdf.

202. University of York, in June of 2013, published results that were similar to those of Oregon Health and Science University. Their review found:

a. The use rhBMP-2 in spinal surgery had modest benefits when compared with ICBG surgery 24 months after surgery;[90]

b. A near doubling in number of cancers with rhBMP-2;[91] and

c. Analyses of adverse event IPD from the Medtronic-sponsored trials showed some complications to be more common among rhBMP-2 patients…Arthritis, implant-related events, retrograde ejaculation, wound complications and neurological, urogenital and vascular events were also more common among rhBMP-2 patients.

203. University of York commented specifically on the reliability of Medtronic's published evidence stating, "we found adverse events to be incompletely and inadequately described in the trial publications."

204. Additionally, "comparing the CSR categories against the adverse events described in published journal articles suggests that **adverse event reporting across the Medtronic publications is relatively sparse and inconsistent**."[92](Emphasis added).

205. Further, University of York found that the **"[p]ublished papers provided far less information than was available** in the confidential CSRs (or in the supplied IPD). The way in which the adverse data were presented in the literature was **highly inconsistent with and the rationale for presenting some adverse events and not others was rarely clear**. Brief, vague statements in some publications that simply noted 'no unanticipated device-related adverse events' were inadequate and unhelpful. In our view, such statements, without supporting evidence, should not be considered acceptable for publication."[93](Emphasis added).

206. University of York stated further that **"[s]tudies published in the wider literature and post marketing data raise concerns** about other adverse events not captured or

[90] *Id.* at 16.
[91] *Id.* at 17.
[92] *Id.* at 100.
[93] *Id.* at 118.

easily apparent in the IPD provided, including heterotopic bone formation, osteolysis, retrograde ejaculation, urinary retention, and dysphagia. Owing the non-randomised nature of the studies and difference between them, **the strength of this body of evidence is weak and findings should be interpreted cautiously**."[94]

207. Other preeminent researchers and scientific journals also weighed in on the study results. Dr. Krumholz of Yale commented on the study findings stating that "**[e]vidence suggests that some data are not missing at random.**"[95]

208. An article addressing the YODA study appeared in the July 23, 2013 edition of *The Journal of the American Medical Association* ("JAMA"). JAMA is the most widely circulated medical journal in the world. The title of the article accurately sums up the results: "Open Access to Data Closes the Book on Efficacy of Popular Bone-Graft Device." The article reports that YODA revealed Infuse® as product "has no clinical advantage over the traditional bone grafting methods." It further reports that both independent Universities found similar results, quoting York University's lead author Mark C. Simmonds; "[w]e think although we had different approaches, we did come up with similar findings [as the Oregon team]." The article reports that "[c]linically, Simmonds could not recommend using rhBMP-2." Finally, the Oregon Health and Science University study team noted "earlier release of all relevant data would have better-informed clinicians and patients making medical decisions."[96] The *JAMA* article is further recognition by the leaders of the medical community that Infuse® was misrepresented by Medtronic and its sponsored authors.

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[94] *Id.* at xvi.

[95] Eugene Caragee, *Response to Long-Awaited YODA Report on Controversial Spinal Fusion Products,* The Spine Journal. (June 17, 2003), *available at* http://www.spine.org/Documents/Carragee_Statement_YODA_Reports_061713.pdf.

[96] Mike Mitka, MSJ, Open Access to Data Closes the Book on Efficacy of Popular Bone-Graft Device, 359-340, (July 24, 2013) JAMA.

e) **Impact of Medtronic's Fraud**

209. Thus MEDTRONIC, while providing spine surgeons with MEDTRONIC-funded studies and published articles purporting to support the efficacy and safety of the off-label uses of Infuse®, simultaneously and systematically concealed adverse events and downplayed other non-MEDTRONIC-funded studies and articles demonstrating serious and frequent adverse events caused by the same off-label uses.

210. Physicians, including Plaintiff's surgeon, Dr. Roger Hartl, were misled by this biased and manipulated medical literature regarding Infuse®. Plaintiff was misled indirectly by virtue of her reliance on her physicians', including Dr. Hartl's, understanding of the risk and benefits of using Infuse®.

211. At all relevant times, MEDTRONIC knew, and/or had reason to know, that its representations and suggestions to physicians that Infuse® was safe and effective for use in off-label surgeries were materially false and misleading; and that physicians like Dr. Hartl would rely on these misrepresentations and omissions in the treatment of their patients, including Plaintiff.

212. MEDTRONIC's specific concealments and misrepresentations, including its distortion of the data concerning the adverse effects of autograph, are described in this complaint. However, Plaintiffs' investigation is ongoing and MEDTRONIC has likely made numerous other misrepresentations

6) **Medtronic Failed to Warn During Its Fraudulent Campaign to Sell Infuse®**

213. Plaintiffs have three theories upon which they allege a claim based on MEDTRONIC's failure to warn. These theories and facts also bolster Plaintiffs' fraud claim.

214. First, MEDTRONIC has failed to satisfy its duty to warn based on its failure to report adverse events to the FDA. This claim mirrors the claim approved by the Ninth Circuit in *Stengel v. Medtronic*, 704 F.3d 1224 (9th Cir. 2013).

215. The allegations supporting Plaintiffs' first theory are as follows. A number of patients have reportedly been harmed in off-label uses of Infuse®. Approximately 844 adverse

events involving Infuse® in spinal surgeries have been reported to the FDA from July 2, 2002 to August 31, 2011.

216. However, as noted earlier, Dr. Carragee and his team discovered specific instances of unreported adverse events related to the use of Infuse® in spinal surgeries. In addition, they estimated adverse events associated with the product ranging from 10 percent to 50 percent depending on the approach used in the spinal surgery. Given the increase in the use of genetically modified bone growth protein in inpatient procedures between October 2002 and December 2007, from 23,900 to 103,194, and that spinal fusion surgeries accounted for 92.8 percent of these procedures, and given that the vast majority of these were off-label uses, Plaintiffs are informed and believe that the adverse events are vastly under reported to the FDA by MEDTRONIC and have been for many years.

217. Plaintiffs are also aware of one instance in which MEDTRONIC failed to timely report the death of a patient resulting from the off-label use of Infuse® as required by FDA regulations and in direct violation of those regulations. By that failure, MEDTRONIC actively concealed the true risk and danger of the product, lulling doctors into believing that the risks posed by the product were not serious or life threatening.

218. Plaintiffs' second theory is that MEDTRONIC had a duty to warn based on nine years of mounting evidence, following the July 2002 PMA approval of Infuse®, that indicated foreseeable dangers facing patients subject to off-label uses of the product. MEDTRONIC was aware of specific risks regarding Infuse®. Yet MEDTRONIC's agents and employees encouraged Opinion Leaders not to include a full accounting of such risks, including known adverse events, in their publications. A surgeon in another case involving Infuse® has also testified that a MEDTRONIC representative told him that the risk of bone overgrown was not a cause for concern in his patient. MEDTRONIC, based on existing studies, knew or should have known about the risks of bone overgrowth, radiculitis and other problems associated with Infuse®.

219. However, instead of warning of such foreseeable risks, MEDTRONIC downplayed and minimized the risks in the medical literature that it manipulated through its paid Opinion Leaders and through misrepresentations made by its employees and agents. As explained further, below, had Plaintiff's surgeon received warnings regarding such risks and a full disclosure of adverse events, he would not have used Infuse® in the manner that he did.

220. Plaintiffs' third theory is that MEDTRONIC had a duty not to deceive. However MEDTRONIC engaged in a pattern and plan of deception intended to result in reliance by the implanting doctors and significantly increased sales and revenue. That plan of deception was, as described above, that MEDTRONIC systematically manipulated the medical literature regarding Infuse® through ghostwriting and by paying Opinion Leaders to create research touting the product and to write and give favorable publicity regarding Infuse® and, thus, misrepresent the product's safety and efficacy.

7) Off-Label Use of Infuse® is Dangerous and Causes Adverse Side Effects.

221. Off-label use of Infuse® was and remains particularly concerning due to the known adverse (and in at least one case deadly) side effects known to MEDTRONIC at the time of the product's original FDA approval in 2002.

222. The off-label use of Infuse® in the spine frequently causes serious adverse events.

223. The FDA Panel's initial fears in 2002 concerning the dangers of off-label use of this product were confirmed by subsequent medical studies that demonstrate that off-label use of Infuse® may present severe risks and dangers to patient safety.

224. For example, an early study sponsored and funded by MEDTRONIC in 1999 demonstrated an approximately 70% rate of ectopic bone growth — meaning bone overgrowth where such growth is not desired. Only a few months into this clinical trial of Infuse®, CT scans showed unwanted bone had formed in the spinal canals of 70% of the patients treated with Infuse®. This clinical trial, intended to include hundreds of people with degenerative disc disease, was halted after only 34 patients were treated with Infuse®.

225. A spine surgeon who participated in this PLIF with Infuse® study reported that one of the patients he treated required two extra surgeries to clear the excessive bone growth from the patient's spinal canal. The complications observed in this PLIF trial were particularly serious given the potential of neural impingement (or nerve pinching) from such bony overgrowth in that procedure, potentially triggering the very sort of pain that a fusion procedure attempts to eliminate.

226. This bone overgrowth results from Infuse®'s very mechanism of action. In such cases, Infuse® can stimulate bone growth where new bone is not desired and can lead to excessive bone growth into areas where bone should not be growing — *i.e.*, into or against the spinal cord or other spinal nerves.

227. There is insufficient scientific evidence concerning the proper dosages of rhBMP-2 for use in the off-label procedures such as PLIF, TLIF, PLF and cervical fusions, or the expected responses to the protein in different biological environments. Indeed, many adverse events associated with the use of Infuse® result from off-label use of the product by surgeons who do not fully understand the highly potent nature of this molecule.

228. A study entitled, "Prevalence, Complications, and Hospital Charges Associated with Use of Bone-Morphogenetic Proteins in Spinal Fusion Procedures," Cahill, et al., *JAMA*, 2009 Jul 1;302(1):58-66, analyzed the integration of BMP into spinal surgeries since 2002, and the association between its use and postoperative complications, length of hospital stays, and hospital charges. Significantly, the study determined that use of bone morphogenetic proteins is associated with a substantially higher rate of complications in anterior cervical fusion procedures, which has resulted in an approximate 41% increase in hospital charges for these procedures. Notably, the study only considered complications that occurred during postoperative inpatient hospitalization immediately following the surgical procedure, and did "not include delayed complications in the outpatient setting," such as hospital readmission-related complications.

229. Such a shortcoming likely resulted in a significant understatement of the extent of complications resulting from use of bone morphogenetic proteins because, as an FDA Public Health Notification regarding complications from use of BMP in the cervical spine indicated, "[m]ost complications occurred between 2 and 14 days post-operatively with only a few events occurring prior to day 2." Indeed, acknowledging this fact, Dr. Kevin S. Cahill, who led the study, publicly commented, "ours is probably a bottom estimate."

230. Aside from potential understatement of complications, the study found that the rate of complications in anterior cervical fusions was 51.4% higher when using bone morphogenetic protein than in similar cases when bone morphogenetic protein was not used. These complications included increased rates of voice and swallowing-related problems, and swelling of the neck. The study's authors noted a "significantly greater" rate of complications when using bone morphogenetic proteins in these surgeries, even after considering and compensating for numerous other variables that could affect complications rates, such as age, sex, etc.

231. Astonishingly, it was not until 2004 that a paper about the disastrous 1999 PLIF trial by spine surgeons with financial ties to MEDTRONIC was finally published in a medical journal. This article inaccurately maintained that these patients were not harmed by Infuse®. The paper (Haid, et al., *Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages, The Spine Journal*, 4(5):527-538, September 2004) downplayed the bone overgrowth complications claiming that while it showed up on CT scans, patients did not suffer ill effects. This claim was false and misleading and further encouraged dangerous off-label uses of Infuse®.

232. In fact, David Malone, M.D., a Tulsa, Oklahoma spine surgeon involved in this 1999 PLIF clinical trial with Infuse®, told the *Milwaukee Journal Sentinel* that two of his patients had to undergo additional surgeries because the BMP-induced bone overgrowth was painfully impinging on their nerve roots. One of the patients, a man who was in his 50s at the time,

needed three operations - one for the implant, a second to remove the unwanted bone formation, and then a third when the additional bone grew back yet again.[97]

233. "It was a pretty amazing biological response," Malone said in an interview. "It grew back even larger than the first time. It got to the point that secretaries in our clinic could look at X-rays and tell who got the BMP (Infuse) and who did not. You could see that much bone growth."[98]

234. A May 15, 2006 medical article in *Spine* entitled "Controlling Bone Morphogenetic Protein Diffusion and Bone Morphogenetic Protein-Stimulated Bone Growth Using Fibrin Glue" observed, "rhBMP-2 may stimulate bone growth in areas in which bone is not desired, especially as the material 'leaks' into such spaces. . . . Although this phenomenon has not been thoroughly studied, it implies that the release of rhBMP-2 into the soft tissues stimulates a rapid, potentially life-threatening, inflammatory reaction." [99]

235. Again, in a November 2006 issue of *Spine*, several authors noted a significantly increased risk of swelling from off-label use of Infuse® in cervical spine fusions compared to traditional fusion surgeries. Of the 234 patients studied, 27.5% of those patients treated with Infuse® had significant swelling after the surgery, while only 3.6% of those patients not treated with Infuse® experienced such a complication. Further analysis demonstrated that "patients receiving rhBMP-2 were ***10.1 times more likely*** to have a swelling complication versus those who did not receive rhBMP-2." (Emphasis added.)[100]

236. A *European Spine Journal* article in August 2007 found that use of Infuse® in certain cervical spine fusions resulted in a statistically significant increase in the number of complications, including dysphagia (difficulty in swallowing) and swelling in the neck area. The

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[97] *See, e.g.*, "Infuse® Cited in Patients' Painful Bone Overgrowth: More Surgery Needed After Use, Surgeon Says," by John Fauber, *Milwaukee Journal Sentinel*, June 27, 2011.
[98] *Id.*
[99] Patel, et al, *Controlling Bone Morphogenetic Protein Diffusion and Bone Morphogenetic Protein-Stimulated Bone Growth Using Fibrin Glue, Spine*, 31(11): 1201-1206, May 2006.
[100] Smucker, et al., *Increased Swelling Complications Associated with Off-Label Usage of rhBMP-2 in the Anterior Cervical Spine, Spine*, 31(24): 2813-2819, November 2006.

authors determined that "[d]ysphagia was a common complication and it was significantly more frequent and more severe in patients in whom rhBMP-2 was used. Post-operative swelling . . . was significantly larger in the rhBMP-2 group." Of the patients evaluated, 85% of those treated with Infuse® reported difficulty swallowing after the surgery; a complication that was far less severe in those not treated with Infuse®. Indeed, one patient required a feeding tube for six weeks after the surgery as a result of the complication. [101]

237. On July 1, 2008, the FDA issued a Public Health Notification to healthcare practitioners entitled "Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion" (the "FDA Notification"), which strongly warned medical professionals who used Infuse® and other BMP products of serious complications that had occurred from the off-label use of these products in the cervical spine.[102]

238. The FDA Notification stated that the agency had received numerous reports of complications from BMP use in the cervical spine that "were associated with swelling of neck and throat tissue, which resulted in compression of the airway and/or neurological structures in the neck. Some reports describe difficulty swallowing, breathing or speaking." The notification further stated that these complications had resulted in "the need for emergency medical intervention," which included "respiratory support with intubation, anti-inflammatory medication, tracheotomy and most commonly second surgeries to drain the surgical site." The FDA Notification concluded that "in light of the serious adverse events described above, FDA recommends that practitioners either use approved alternative treatments or consider enrolling as investigators in approved clinical studies."

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[101] Vaidya, et al., *Complications of Anterior Cervical Discectomy and Fusion Using Recombinant Human Bone Morphogenetic Protein-2, European Spine Journal,* 16(8): 1257-1265, March 2007.

[102] FDA Public Health Notification: Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion, July 1, 2008, http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062000.htm

239. On September 4, 2008, *The Wall Street Journal* published a front-page article entitled "MEDTRONIC Product Linked to Surgery Problems."[103] This article noted both the complications resulting from the use of Infuse® in the cervical spine already disclosed in the FDA Notification and additional complications resulting from other off-label applications of the product, stating:

> The FDA's alert about Infuse® was specific to neck surgeries. But a review of FDA records and medical literature shows there have been scores of other cases in which serious complications arose after the product was used in other off-label situations. Many of these cases involve unwanted bone growth near nerves or in areas outside targeted fusion sites. That can lead to pain, repeat surgeries and, in some cases, emergency intervention.

The article further stated that at least three-quarters, or 75%, of the adverse events reported to the FDA involved off-label use of Infuse®. Of course, this news had serious implications for MEDTRONIC because off-label use of Infuse® accounted for the majority of all Infuse® sales.

240. A September 2008 article in *The Spine Journal* also observed that the use of Infuse® in the cervical spine "has been associated with reports of serious adverse events.[104] Postoperative hematoma formation [a collection of blood outside the blood vessels, generally manifesting as bruises], prevertebral soft tissue swelling, [and] swallowing difficulty . . . are a few examples." Of the complications observed in this patient study group, 17% occurred in patients treated with traditional techniques, while 83% occurred in patients treated off-label with Infuse®. The authors concluded that the "cervical spine has proven much less forgiving with the institution of rhBMP-2 use. Complications induced by . . . rhBMP-2 were clearly evident in our review."

241. On November 18, 2008, in connection with reporting MEDTRONIC's financial results for its 2009 second quarter (ended October 24, 2008), MEDTRONIC reported that revenue from its Spinal segment had, in fact, declined to $829 million for the quarter – down $30

[103] "Medtronic Product Linked to Surgery Problems," by David Armstrong and Thomas M. Burton, *Wall Street Journal*, September 4, 2008.
[104] Hartl, et al., *Complications of BMP Use in Cervical Spine Surgery, The Spine Journal,* 8(5): 23S-24S, September 2008.

million from the previous quarter. The decreased sales in the Spinal segment, clearly stemming from a significant decline in Infuse® sales, were a sharp deviation from MEDTRONIC's reports of repeated, double-digit, growth in the Spinal segment in previous quarters. Moreover, MEDTRONIC disclosed, for the first time, that it "recently received a subpoena from the Department of Justice looking into off-label use of Infuse®."

242. Thereafter, MEDTRONIC continued to report lower sales of Infuse®, which it admittedly linked to a public health notice from the FDA regarding off-label use of recombinant human bone morphogenetic protein in the cervical spine that was issued in July 2008, a previously disclosed government investigation, negative newspaper stories, and a whistleblower lawsuit filed by two former MEDTRONIC employees against MEDTRONIC and a number of spine surgeons and distributors of the Infuse® bone graft.

243. The use of Infuse® in off-label procedures was further scrutinized in a study published in the July 1, 2009 issue of JAMA that documented the health risks associated with off-label use of Infuse® and, contrary to previous studies conducted by MEDTRONIC-funded physicians, cast doubt on the cost-effectiveness of the product.[105]

244. MEDTRONIC dramatically under-reported to the FDA adverse events associated with Infuse® from 2002 to at least 2011.

245. From 2002 to 2013, only 6,252 reports of adverse events involving Infuse® were reported to the FDA, many of which were not reported by MEDTRONIC, but instead, by health care practitioners or spine patients.

246. Between 2012 and 2013, however, the number of reports of adverse events involving Infuse® sky-rocketed. In 2011, 289 Infuse®-related adverse events were reported. In 2012, 1,929 reports of Infuse®-related adverse events were reported, a 6-fold (approximately 667%) increase. And in 2013, 3,151 Infuse®- related adverse events were reported, an almost 2-fold (approximately 163%) increase. Thus, 5,080 Infuse®-related adverse events were reported

[105] Cahill, et al., *Prevalence, Complications, and Hospital Charges Associated with Use of Bone-Morphogenetic Proteins in Spinal Fusion Procedures*, JAMA, 302(1): 58-66, July 2009.

in just the past two years, 2012 and 2013. In other words, more than 81% of the total cumulative adverse events associated with Infuse® reported to FDA were reported in the past two years.

247. This increase is in spite of the nationwide decline in the use of Infuse® in spine patients after the publication of the revelatory findings in the June 2011 issue of *The Spine Journal*, suggesting widespread underreporting of adverse events in the years prior, from 2002 to 2011. Indeed, MEDTRONIC'S sales of Infuse® have gradually declined each quarter since the release of the June 2011 *Spine Journal* articles, which set off a firestorm of controversy in the world of spine surgery regarding ethical and patient safety concerns over off-label use of Infuse® in the spine.

248. The vast majority of these adverse event reports involve off-label use of Infuse®. In fact, in a 2012 article published in *The Spine Journal*, FDA researcher Emily Woo, M.P.H. concluded on-label use of Infuse® accounts for only a tiny percentage (0.5%) of adverse events. Off-label use of Infuse® accounts for 99.5% of adverse events.[106]

249. Despite the recent spike in reports of adverse events involving Infuse® to the FDA, the overall number is unexpectedly low when compared with the estimated predicted number of Infuse®-related adverse events and Infuse®-related adverse events involving off-label applications.

250. As illustrative of this point, the scientific literature suggests that: (1) since 2007, there may be as many as 400,000 spinal fusions performed in the United States in any given year;[107] (2) since 2007, there may be as many 100,000 procedures performed each year in the United States involving Infuse®, of which 92.8% are spinal fusions,[108]; and (3) approximately

[106] Emily Jane Woo, *Recombinant Human Bone Morphogenetic Protein 2: Adverse Events Reported to the Manufacturer and User Facility Device Experience Database*, The Spine Journal, 12(10): 894-899, October 2012.

[107] According to national epidemiological data, the number of spinal fusion discharges in the United States increased 2.4 fold (137%) from 174,223 to 413,171 from 1998 to 2008. *See* Rajaee SS et al., *Spinal fusion in the United States: analysis of trends from 1998 to 2008*, The Spine Journal, 37(1): 67-76, February 2012.

[108] According to national epidemiological data, the number of procedures performed in the United States each year from 2003-2007 involving Infuse® increased 4.3 fold from 23,900 to

85% of procedures performed involving Infuse® in the United States in any given year are off-label applications.[109]

251. Thus, in any given year since 2007, the annual estimated number of spinal fusions involving off-label use of Infuse® is likely in the neighborhood of 78,000.[110]

252. The scientific literature (e.g., Carragee, et al.[111]) has reported that the actual incidence of adverse events associated with Infuse® in spinal fusions is between 10% to 50%, varying with the type of procedure. Accounting for the fact that off-label use of Infuse® accounts for 99.5% of the Infuse® adverse events, the estimated incidence of adverse events attributable to the off-label use of Infuse® in spinal fusions remains between roughly 10%[112] and 50%[113].

253. Thus, in any given year since 2007, the annual estimated predicted number of adverse events attributable to the off-label use of Infuse® in spinal fusions likely ranges from 7,761[114] to 38,805[115]. Additionally, since 2007, the total predicted number of adverse events

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103,194. *See* Ong KL, et al., *Off-label use of bone morphogenetic proteins in the United States using administrative data*, The Spine Journal, 35(19): 1794-800, September 2010.

[109] *See* Ong KL, et al., *Off-label use of bone morphogenetic proteins in the United States using administrative data*, The Spine Journal, 35(19): 1794-800, September 2010.

[110] 100,000 (estimated number of procedures performed each year in the U.S. involving Infuse®) x .928 (estimated percent of spinal fusions of the procedures performed each year in the U.S. involving Infuse®) x .85 (estimated percent of procedures performed involving Infuse® in the U.S. each year that are off-label applications)= 78,880 spinal fusions involving off-label uses of Infuse®

[111] Eugene J. Carragee, Eric L. Hurwitz & Bradley K. Weiner, *A Critical Review Of Recombinant Human Bone Morphogenetic Protein-2 Trials In Spinal Surgery: Emerging Safety Concerns And Lessons Learned*, The Spine Journal, 11, 471-491 (2011).

[112] .10 (estimated percent of incident of adverse events attributable Infuse® in spinal fusions) x .995 (estimate percent of adverse events involve off-label use of Infuse®) x 100 = 9.95%.

[113] .50 (estimated percent of incident of adverse events attributable Infuse® in spinal fusions) x .995 (estimated percent of adverse events involve off-label use of Infuse®) x 100 = 49.975%.

[114] 78,000 (estimated number of spinal fusions involving off-label use of Infuse® in any given year) x .0995 (estimated percent of the actual incident of adverse events attributable to Infuse®) = 7,761.

[115] 78,000 (estimated number of spinal fusions involving off-label use of Infuse® in any given year) x .4975(estimated percent of the actual incident of adverse events attributable to Infuse®) = 38,805.

attributable to the off-label use of Infuse® in spinal fusions most likely ranges from 54,327[116] to 271,635,[117] varying with the type of procedure. Even assuming that off-label uses (which gradually increased from 2002 to at least 2011) did not reach significant levels until 2005 or 2006, there should be many more adverse event reports made to the FDA during the time period that Infuse® has been on the market.

254. That there have only been a total of 6,252 reports of adverse events involving Infuse® reported to the FDA from 2002 to 2013 (a vast majority of which involve off-label use), and that from 2002 to 2010 there were only approximately 1,172 adverse events reported to the FDA, creates a compelling inference that MEDTRONIC failed to report significant numbers of adverse events associated with Infuse® and known to it from 2002 to at least 2011.

255. As discussed and demonstrated herein, the number of Infuse®-related adverse events is growing steadily over the years, and the proportion of off-label adverse events grows, as well, as a direct result of the MEDTRONIC Defendants' long-standing campaign of improper off-label promotion of the more dangerous off-label uses of Infuse® which were never approved by the FDA. The extent of these adverse events were, at all relevant times, hidden or downplayed by MEDTRONIC and its paid consultants.

8) MEDTRONIC's Prior Knowledge and Concealment of the Dangers of Off-Label Infuse® Uses.

256. Even at the time of FDA approval, MEDTRONIC and its senior management and its paid consultant "opinion leaders," were well aware of the concerns regarding off-label uses of Infuse® and the serious dangers to patients posed by those off-label uses.

257. Notwithstanding the original FDA Panel's well-founded concerns regarding off-label use, as well as the medical literature's corroboration of the same, both of which MEDTRONIC had knowledge of, MEDTRONIC intentionally, negligently and recklessly

[116] 7,761(estimated predicted number of adverse events attributable to Infuse® in spinal fusions in any given year) x 7 (2007-2014) = 54,327.
[117] 38,805 (estimated predicted # of adverse events attributable to Infuse® in spinal fusions in any given year) x 7 (2007-2014) = 271,635.

concealed these dangers from the general public, including the Plaintiff and Plaintiff's physicians.

258. MEDTRONIC had actual knowledge of the Advisory Committee's concerns regarding off-label use of the product and the dangers posed by off-label use. Indeed, Defendants were on actual notice at this time of the Advisory Committee's warnings that MEDTRONIC should guard against off-label uses of this potent genetically-engineered liquid bone protein. Thus, even *prior* to FDA approval, Defendants were on actual notice of the dangers that off-label use of Infuse® posed to patients, such as the Plaintiff.

259. Further, as described immediately *infra*, the MEDTRONIC-funded studies on Infuse® from 1999 to until at least 2007 failed to accurately describe the adverse effects that were observed in the earliest trials of Infuse®, such as severe uncontrolled or ectopic bone growth, severe inflammatory reactions, adverse back and leg pain events, radiculitis, retrograde ejaculation in men, urinary retention, bone resorption, and implant displacement. These MEDTRONIC-funded articles also omitted any mention of the risks of sterility and cancer associated with rhBMP-2 use, as reported in FDA documents and hearings. MEDTRONIC discouraged the publication of these results in the medical journal literature, thereby hiding significant side effects from spine surgeons and patients.

260. Further, Confidential Witness 2 ("CW 2") in a shareholder derivative lawsuit filed against MEDTRONIC, more fully discussed *supra*, stated that MEDTRONIC was aware of adverse events resulting from off-label use of Infuse® in the cervical spine, including swallowing, and breathing problems.

261. In response to these reports of adverse events, CW 2 stated that MEDTRONIC attempted to disseminate information to the medical community regarding what it considered to be the proper dose of Infuse® for this off-label application. MEDTRONIC also issued a "Safety Alert" letter to surgeons on September 14, 2004, informing them that MEDTRONIC had received reports of complications associated with off-label use of Infuse® in anterior cervical fusion procedures. MEDTRONIC wrote, "***[l]ocalized soft tissue edema has been reported in***

anterior cervical spine fusion surgery following the use of Infuse® Bone Graft.... Some reports were accompanied by patient complaints of swelling and difficulty in swallowing and breathing, three of which resulted in surgical intervention." (Emphasis added.)

262. These adverse events were not isolated incidents, as described above. These adverse event reports from off-label uses of Infuse® indicate the very same complications as those noted in the studies discussed above, including, swelling, difficulty swallowing and breathing, excessive bone growth resulting in dangerous and painful spinal nerve compression and corresponding injuries, etc., and often require emergency medical intervention or a second surgery.

263. For example, a December 12, 2005 report indicates that four or five days after an off-label PLIF procedure using Infuse®, the patient's swelling became so severe that surgical intervention was required. These are only a few examples of the hundreds of similar reports of serious complications related to off-label uses of Infuse® found on the MAUDE Database.

264. A November 3, 2006 report indicates that a patient reported neck swelling, difficulty swallowing and possible shortness of breath two to three days after a cervical spine fusion using Infuse®. As a result, this patient had to undergo another surgery four days after the initial fusion.

265. A July 21, 2008 report indicates that a patient developed massive neck swelling, very thick tracheal and bronchial secretions, and required a tracheostomy—a procedure in which an incision is made in the neck and a tube inserted to allow the patient to breathe—following a cervical fusion procedure with Infuse®.

266. Through MEDTRONIC's monitoring procedures—which include written procedures for complaints, corrective and preventative actions and adverse event reporting—all complaints and adverse events are documented, tracked, and trended (or should be) in a database. MEDTRONIC is required by federal regulation to "establish and maintain" such an adverse event database. *See* 21 C.F.R. § 803.1(a). In addition, a report from a June 2006 FDA inspection of a MEDTRONIC facility at 1800 Pyramid Place in Memphis, Tennessee, revealed

that MEDTRONIC had initiated a Preventative Action, dated April 21, 2006, and was "studding [sic] the reason for an increase in the number of reported fluid collection, hematoma, and seroma complaints since 4/2005." According to the report, the "study indicated that sales for the Infuse® Bone Graph [sic] have increased and more graphs [sic] are being implanted," and that the "study is still open."

267. According to Confidential Witness #15 ("CW 15") in the *Minneapolis Firefighters* lawsuit filed against MEDTRONIC, more fully discussed *supra*, a Senior Vice President who worked at MEDTRONIC for numerous years until 2006 and a "Quality Group" at MEDTRONIC's Spine division were responsible for addressing adverse events. According to CW 15, former COO Michael DeMane, former President of MEDTRONIC Spinal and Biologics Mr. Wehrly, and former Worldwide Vice President and General Manager, Biologics, Jon Serbousek, were all aware of the adverse events related to Infuse®. As a part of his employment with Defendants, CW 15 discussed the complaints related to Infuse® at meetings with these individuals and members of the Quality Group to decide whether or not certain adverse events should be reported to the FDA. Moreover, MEDTRONIC's Spinal division used the very same complaint/adverse event reporting system as MEDTRONIC corporate, which provided MEDTRONIC's executive officers access to a database containing details of every complaint/adverse event MEDTRONIC received relating to Infuse®.

268. MEDTRONIC was further clearly aware of its settlement with the Department of Justice ("DOJ") and entry into a Corporate Integrity Agreement, discussed *supra*, in July of 2006. As a result, MEDTRONIC had actual knowledge of the heightened risks to spine patients associated with MEDTRONIC's illegal, improper, and unethical promotion of off-label use of Infuse® by MEDTRONIC's Spinal or Biologics Divisions.

9) Off-label Promotion of Infuse® Significantly Impacted the Market

269. Off-label use of Infuse® increased year-after-year from the time of its original limited use approval by the FDA in 2002, to the point where off-label use of Infuse® Bone Graft accounted for an astounding 85% to 90% of all Infuse® sales.

270. Although undisclosed by MEDTRONIC, the first-hand accounts of its former employees demonstrate that this extraordinarily high off-label use was driven by MEDTRONIC's sales force. Specifically, MEDTRONIC's marketing and sales employees directed spine surgeons to MEDTRONIC-compensated consultants or "Opinion Leaders" or "Thought Leaders" – other spine surgeons paid by enormous sums of money by MEDTRONIC – the sole purpose of which was to promote off-label uses of Infuse®. Through these and other illegal and improper practices, MEDTRONIC was able to increase Infuse® sales year after year while continuing to hide and downplay the product's dangerous side effects when used off-label in the spine.

271. Several spine surgeons have already testified under oath at depositions that MEDTRONIC sales personnel overtly and directly promoted to them the off-label uses of Infuse® in the spine, and Plaintiffs are thus informed and believe that MEDTRONIC engaged in a scheme at all relevant times to expand its market share of this product by improperly encouraging such off-label uses.

272. In this particular case, MEDTRONIC actively promoted the off-label procedures to Plaintiff's spine surgeon, and Plaintiff's spine surgeon would not have performed the off-label Infuse® procedure in the absence of such promotion. MEDTRONIC's off-label promotion of Infuse® to Plaintiff's surgeon was false and misleading, in that it overemphasized the purported benefits of the off-label use, and hid, minimized, or downplayed the true risks and dangers of the off-label use, all of which were known to MEDTRONIC at all relevant times.

10) MEDTRONIC's Off-Label Promotion Practices Have Led to Whistleblower and Shareholder Litigation and Federal Investigations

273. MEDTRONIC's unlawful off-label promotion campaign has been so extensive that it caught the attention of, among others, the FDA, the United States DOJ, Congress, the United States Army, several major universities, multiple medical journals, numerous major newspapers, independent physicians, and investors.

274. Moreover, MEDTRONIC's unlawful off-label campaign has resulted in, among other actions, two whistleblower lawsuits (resulting in a multi-million dollar settlement with the DOJ, which included a Corporate Integrity Agreement), a shareholder derivative lawsuit that was recently settled for $85 million, several adverse regulatory actions by the FDA, and a congressional investigation (led by the United States Senate Committee on Finance).

a) Whistleblower Lawsuits Resulting in a Corporate Integrity Agreement

275. MEDTRONIC Defendants were named as defendants in two *qui tam* actions, *United States ex rel. (UNDER SEAL) v. MEDTRONIC. Inc., et al.*, Civil Action No. 02-2709 (W. D. Tenn. 2002) (hereinafter "*[Under Seal]*"), and *United States ex rel. Poteet v. MEDTRONIC, Inc., et al.*, Civil Action No. 03-2979 (W. D. Tenn. 2003) (hereinafter "*Poteet I*"), (collectively the "qui tam lawsuits"), both of which alleged that MEDTRONIC violated the False Claims Act, 31 U.S.C. § 3729, *et seq.*, by paying illegal kickbacks to physicians in connection with promoting the off-label use of Infuse® in the spine, which resulted in the submission of false or fraudulent claims to federal health care programs.

276. Based on its investigation, the DOJ contended that certain of the payments, services, and remuneration mentioned above were improper and resulted in the submission of false or fraudulent claims in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b), *et seq.*, which prohibits individuals from offering, soliciting or making any payment or remuneration to induce business reimbursed under a federal or state health care program, and the False Claims Act, 31 U.S.C. § 3729, *et seq.*, which provides penalties for the submission of false claims to the federal government. Both *[Under Seal]* and *Poteet I* were brought by MEDTRONIC's former employees who made these allegations.

277. In these lawsuits, the DOJ contended that between January 1, 1998 and April 30, 2003, MEDTRONIC made payments and provided other remuneration to a number of physicians and entities in connection with its spinal products in the form of (1) payments and other remuneration for physicians' attendance and expenses at medical education events, "think tanks," VIP/opinion leader events, and meetings at resort locations; (2) services and payments

for services to physicians through MEDTRONIC's Healthcare Economic Services and eBusiness Departments; and (3) payments made pursuant to consulting, royalty, fellowship and research agreements with various physicians and entities

278. Specifically, *[Under Seal]* was brought by a former MEDTRONIC in-house counsel, who alleged that MEDTRONIC's "aggressive and illegal" sales and marketing efforts were intended by MEDTRONIC to improperly induce physicians to use MEDTRONIC's Spinal products, including Infuse®. The conduct alleged included, *inter alia*: (1) lucrative consulting and royalty agreements with physicians that used MEDTRONIC Spinal products, "the true purpose [of which were] to funnel money to the physicians so that they will be induced to use [MEDTRONIC Spinal] products;" and (2) "[l]avish all-expense paid trips to fine resorts . . . disguised as Medical Education seminars, think tanks, or discussion groups . . . held in places such as Hawaii, Cancun, Alaska, Beaver Creek, Whistler, Malaysia, Amelia Island, Teton Valley, and New Orleans at Mardi Gras . . . [t]he purpose of these lavish trips was to induce the physicians to use [MEDTRONIC Spinal] products."

279. The complaint further alleged that: "Most of the illegal kickback practices described herein were begun by Sofamor Danek and continued by [MEDTRONIC] after the acquisition. Kickbacks were the culture and way of doing business at Sofamor Danek and the company was determined to continue that culture, and did continue that culture, when Sofamor Danek became part of the MEDTRONIC empire."

280. *Poteet I* brought by a former MEDTRONIC employee who was tasked by MEDTRONIC to arrange travel (including expense reimbursement) for numerous spinal surgeons to attend MEDTRONIC-sponsored events and other professional meetings. This former employee also alleged that MEDTRONIC paid surgeons substantial fees—sometimes up to hundreds of thousands of dollars per year—for consulting services that were grossly in excess of their fair market value, entered into royalty agreements that were designed to disguise illegal remuneration, and provided physicians opportunities for lavish travel and recreational activities, including "upgraded lodging for physicians, dinners, entertainment and activities such as golf,

snorkeling, sailing, fishing, shopping trips, [and] horse-back riding" for using MEDTRONIC products. These consulting agreements and other payments were illegitimate means of inducing physicians to use MEDTRONIC products and to recommend to other physicians that they do the same.

281. On July 18, 2006, MEDTRONIC agreed to pay $40 million to the United States of America to settle these lawsuits under the False Claims Act, 31 U.S.C. §§ 3729-3733, the Civil Monetary Penalties Law, 42 U.S.C. § 1320a-7a, and the Program Fraud Civil Remedies Act, 31 U.S.C. §§ 3801-12.

282. As part of the DOJ settlement, MEDTRONIC agreed to enter into a five-year Corporate Integrity Agreement ("CIA") with the Office of the Inspector General/Health and Human Services that, as MEDTRONIC described in its July 18, 2006 press release, implemented substantial oversight structures and procedures meant to ensure "top-level attention to corporate compliance measures." Among other things, the CIA required MEDTRONIC to establish an electronic database to capture and manage all non-sales related transactions between MEDTRONIC's Spinal segment and its physicians or customers, with all such transactions subject to an established set of internal controls and review processes, including monitoring by MEDTRONIC senior management and MEDTRONIC's Chief Compliance Officer.

283. Moreover, the CIA required MEDTRONIC to implement internal policies and procedures to ensure stricter regulatory compliance, which obligated MEDTRONIC to institute a number of changes to improve oversight of its Spinal division.

284. Significantly, the CIA required MEDTRONIC to adopt procedures to ensure that any "arrangements"—a term intended to cover physician consulting agreements and broadly defined as engagements involving "directly or indirectly, the offer, payment, solicitation, or receipt of anything of value; [] between [MEDTRONIC] and any actual or potential source of health care business [e.g., physicians]"—would not violate federal law. Such procedures were to include, among other things: (1) creating a database of all existing and new or renewed arrangements; (2) tracking remuneration from MEDTRONIC to all other parties to such

arrangements; (3) tracking service and activity logs to ensure that parties to an arrangement are performing their duties under the applicable arrangement; (4) implementing procedures that ensure all arrangements are reviewed for adherence to the Anti-Kickback Statute; and (5) regular (at least quarterly) review by the MEDTRONIC Compliance Officer of the arrangements database along with reporting (at least quarterly) to the MEDTRONIC Compliance Committee.

285. The CIA and the previous whistleblower litigation placed MEDTRONIC and its agents on actual notice that its practice of marketing, and promoting Infuse® for off-label uses was improper and required wholesale change to avoid further adverse regulatory action or other liability.

286. As a result of this settlement, MEDTRONIC agreed to negotiate with representatives of the National Association of Medicaid Fraud Control Units to reach an agreement that provides for distribution of certain sums to the several states with which MEDTRONIC agreed to a settlement concerning the conduct at issue in the False Claims lawsuits.

287. Nonetheless, MEDTRONIC's unlawful practices continued, as did MEDTRONIC's aggressive efforts to drive Infuse® sales by promoting off-label applications, such as precisely those used on the Plaintiff. MEDTRONIC has continued to improperly and illegally promote the off-label use of Infuse® for non-FDA-approved uses of the product. Indeed, it was motivated to do so knowing that, absent off-label use, sales of Infuse® would dramatically decline. In order to prevent a decline in sales revenue, MEDTRONIC continued to covertly employ the same lucrative "consulting" arrangements and other unlawful conduct to promote off-label uses of Infuse®.

288. As a result of MEDTRONIC's undisclosed misconduct, the percentage of off-label Infuse® usage increased over time, including after the DOJ settlement on July 14, 2006. By 2011, off-label use of Infuse® constituted more than 90% of the total use of Infuse® in spinal fusion procedures.

289. Indeed, MEDTRONIC's unlawful marketing and promotion was so effective that a MEDTRONIC analyst from Bernstein Research noted in a November 21, 2006 report that analysts were "expecting *continued indication expansion (e.g., recent dental approval and likely approval for posterior lateral fusion) for Infuse® to be the main driver for the spinal business* in the mid-term." (Emphasis added.) What this analyst and the public at large did not know was that, despite the limited FDA-approved applications of Infuse®, MEDTRONIC continued to drive sales solely through off-label indications; and was doing so in spite of the CIA, the material risk of further regulatory action or other liability, and in conscious disregard for the health and welfare of spine patients such as Plaintiff LIGIA VANESSA CHAPETON.

b) Shareholder Derivative Action Against Medtronic.

290. A federal securities lawsuit filed on behalf of the Minneapolis Firefighters' Relief Association against MEDTRONIC, *Minneapolis Firefighters' Relief Assoc. vs. MEDTRONIC, Inc.*, Civil No. 08-6324 (PAM/AJB) (D.Minn., 2009), also alleged evidence of MEDTRONIC's egregious campaign of off-label promotion of Infuse®, even after the CIA. MEDTRONIC's actions, described by the "Confidential Witnesses" ("CW"), included:

a. MEDTRONIC-sponsored physician meetings, during which MEDTRONIC would employ paid consultants – typically surgeons hand selected by MEDTRONIC – to present off-label presentations to local physicians. CW1, Consolidated Class Action Complaint dated August 21, 2009, at ¶ 93.

b. MEDTRONIC's instructions to its sales representatives regarding various off-label uses of Infuse®, including how much of the biologic to use with off-label cervical fusions, the purpose of which was to instruct physicians regarding off- label uses. CW1, *Id.* at ¶ 94.

c. MEDTRONIC's directions to its sales representatives that they be present during off-label Infuse® surgeries "to assist and direct and give advice when asked." CW1, *Id.* at ¶ 95; CW2, *Id.* at ¶ 97; CW5, *Id.* at ¶ 101; CW6, *Id.* at ¶ 102.

d. MEDTRONIC's creation of sales quotas that were described by the CWs as impossible to reach without pushing off-label use. CW1, *Id.* at ¶ 95; CW9, *Id.* at ¶ 105; CW11, *Id.* at ¶ 107; CW12, *Id.* at ¶ 108.

e. MEDTRONIC sales representatives' references to data from published literature (presumably funded by MEDTRONIC) when questioned by surgeons, the purpose of which was to provide surgeons with information regarding proffered techniques for off-label procedures and to educate them regarding off-label uses. CW2, *Id.* at ¶ 96.

f. MEDTRONIC's development of smaller-sized Bone Graft kits under the guise of selling them for FDA-approved uses, when, in actuality, MEDTRONIC had designed them to be used in off-label cervical fusion surgeries. CW2, *Id.* at ¶ 97; CW7, *Id.* at ¶ 103.

g. Moreover, by comparing the number of units of rhBMP-2 with the sales of the LT-Cage™ component – which were packaged and sold separately – CW2, 11, and 12 determined that the driving force behind MEDTRONICs $750 million in sales of Infuse® was solely attributable to off-label uses. Although the FDA required the rhBMP-2 and LT-Cage™ to be used together, sales of the rhBMP-2 component greatly outpaced those of the LT-Cage™. component. CW2, *Id.* at ¶ 98; CW11, *Id.* at ¶ 107; CW12, *Id.* at ¶ 108.

h. When questioned by a physician about how to use Infuse® off-label, MEDTRONIC sales representatives directed physicians to other surgeons who used the product off-label and also would demonstrate or explain how to do so. CW3, *Id.* at ¶ 99; CW5, *Id.* at ¶ 101; CW6, *Id.* at ¶ 102; CW10, *Id.* at ¶ 106; CW11, *Id.* at ¶ 107.

i. MEDTRONIC held quarterly meetings in at least one sales region, during which a national biologics specialist would attend to explain how to conduct off-label applications of Infuse®. CW3, *Id.* at ¶ 99.

j. MEDTRONIC directed its sales representatives to instruct physicians to use half the dose of rhBMP-2 during cervical fusion, and MEDTRONIC, aware of adverse events, instructed the representatives to tell physicians to use steroids to combat potential inflammation. CW4, *Id.* at ¶ 100; CW5, *Id.* at ¶ 101.

k. MEDTRONIC directed physicians using the product in cervical spine fusion to throw away a large portion, sometimes up to half, of the rhBMP-2 dosage. CW6, *Id.* at ¶ 102.

l. MEDTRONIC gave to physicians a small book containing no reference to MEDTRONIC, which contained information regarding the volume or dosage of rhBMP-2 that should be used for off-label applications of Infuse®. CW7, *Id.* at ¶ 103; CW8, *Id.* at ¶ 104; CW9, *Id.* at ¶ 105.

m. MEDTRONIC instructed CW8 and others during sales presentations regarding how to "get around" restrictions on off-label promotion. CW8, *Id.* at ¶ 104.

n. CW13 was brought into MEDTRONIC to develop a marketing plan; which included: a) Development of a "referral marketing" campaign designed to promote the product for off-label uses via a physician referral network; b) identifying which surgeons would be targeted as part of MEDTRONIC's off-label campaign and what claims MEDTRONIC would make about the product; c) development of a "cookie- cutter" CD series that outlined MEDTRONIC's off-label campaign and included information on off-label procedures that was distributed to MEDTRONIC sales representatives. According to CW13, the referral marketing program involved having surgeons meet with other surgeons as a means of prompting discussion of off-label uses of Infuse® Bone Graft among practitioners. CW13 also stated that MEDTRONIC used a physician training program involving cadaver labs as a means to instruct surgeons regarding off-label applications. CW13, *Id.* at ¶ 109.

o. CW13 was rebuffed for raising concerns about off-label promotion, and was told "we're paying you a lot of money to launch this. Shut your mouth and take the money. Let us worry about what is off-label or isn't." CW13, *Id.* at ¶ 110.

p. A sales representative was present in the operating room during an off-label cervical procedure which led to the patient's death. The patient's family subsequently initiated civil litigation against MEDTRONIC and the sales representative who was allegedly encouraging the off-label procedure at MEDTRONIC's behest. *Id.* at ¶ 111.

q. Although MEDTRONIC is under an obligation to report all serious adverse events associated with Infuse®, MEDTRONIC failed to report the death of this patient until three months after it occurred. FDA guidelines recommend that a manufacturer make a minimum of three attempts to retrieve additional information regarding any adverse event. While the company filed an adverse event report with the FDA in which it noted the complications immediately following the procedure, MEDTRONIC did not inform the agency of her death until after a lawsuit was filed by the patient's family and reported in *The Wall Street Journal*. *Id.* at ¶ 112.

r. In a separate civil suit against MEDTRONIC, a physician admitted to attending numerous national spine meetings during which off-label uses of rhBMP-2 in the cervical spine were promoted. A MEDTRONIC sales representative was in the operating room a lot when he was performing off-label uses. He admitted to doing over 100 cervical procedures, insinuating that the MEDTRONIC sales representative was in the room for a fair number of these procedures. *Id.* at ¶ 113.

291. The plaintiffs in the *Minneapolis Firefighters* lawsuit also discovered the growing percentage of off-label Infuse® usage from 2003-2007 by analyzing surgical procedural codes used by hospitals.[118] The results of this analysis demonstrate that off-label usage of Infuse® was high, even from the inception of FDA approval, and increased by an astonishing 10% over the next 4 years; to wit:

Year	Estimated On-Label Procedures	Estimated Off-Label Procedures
2003	25.7%	74.3%
2004	20.6%	79.4%
2005	15.8%	84.2%
2006	15.3%	84.7%
2007	14.8%	85.2%

[118] The methodology employed was consistent with a July 1, 2009 report in the JAMA that conducted a retrospective cohort study of 328,468 patients undergoing spinal fusion procedures from 2002-2006, using the same codes from the NIS database.

292. Moreover, the data further demonstrate that off-label use of Infuse® in the cervical spine grew to as much as 18% of overall Infuse® use as of 2007, despite the known increased medical risks associated with that application.

293. Indeed, to set sales projections for Infuse®, CW 2 stated that MEDTRONIC's marketing department accounted for the scope and number of procedures performed, including the numbers of off-label procedures, such as PLIFs and TLIFs, to predict sales projections. This analysis was based, in part, on data purchased from market research companies demonstrating the number of procedures involving different areas of the spine, e.g., certain lumbar (on- or off-label) versus cervical (off-label). Once MEDTRONIC determined its sales projections, these figures were incorporated into a budget presented to MEDTRONIC's senior management. Importantly, the final sales quotas for Infuse® were dictated by MEDTRONIC senior management, and were far in excess of what MEDTRONIC's Spinal Division had projected, or could be achievable absent promotion of the product for off-label uses. According to CW 2, "when the numbers came back down, they never reflected the projections. They were much larger."

294. Numerous confidential witnesses, including CWs 1, 9, 12 and CW 14 (a senior manager for MEDTRONIC's Spinal and Biologics division from 2005 to 2008), confirm the intense pressure MEDTRONIC's management placed on its sales representatives to meet the sales quotas the company set. Like CW 2, CW 14 explained that sales goals were set by a handful of MEDTRONIC executives, and that they were "very, very, very aggressive." Likewise, CW 12 stated that there was a lot of pressure on MEDTRONIC's Spinal and Biologics division to reach unreasonable sales targets.

295. As demonstrated, by years 2006-07, off-label uses accounted for an astounding 85% of Infuse® sales; a fact known or recklessly disregarded by all employees, who reviewed marketing data and analyses to set sales quotas for Infuse®. Indeed, sales quotas for Infuse® required sales to grow 20% year-over-year, and MEDTRONIC knew that such increases could

not be achieved without substantial off-label sales, and thus that such aggressive targets would encourage off-label promotion by its employees and representatives.

296. In June 2011, one of the leading journals on spine surgery, *The Spine Journal*, described more fully *supra*, devoted an entire issue to publishing various articles regarding the risks associated with Infuse®, including articles on MEDTRONIC's failure to accurately report the side effects from its clinical trials; MEDTRONIC's failure to report that many of the authors who studied and promoted Infuse® had significant financial ties to MEDTRONIC, with a median range of $12 to $16 million per study; that Infuse® can cause severe injuries to the spinal nerves and spinal cord; that off-label use of Infuse® can lead to other severe side effects; and that MEDTRONIC and its paid consultants/study authors downplayed the risks associated with Infuse®, over-emphasized its benefits and over-emphasized the risks associated with traditional non-Infuse® spine fusion procedures.

c) U.S. Senate Investigation

i) September 30, 2008 Letter.

297. Despite the July 2006 Settlement with the DOJ, concerns regarding MEDTRONIC's off-label marketing activities and related payments to doctors continued.

298. On September 30, 2008, U.S. Senator Herb Kohl sent a letter to MEDTRONIC noting that earlier in 2008, MEDTRONIC's outside counsel provided to the Special Committee on Aging a written account of MEDTRONIC's efforts to comply with the July 2006 Settlement Agreement it reached with the DOJ concerning allegations that MEDTRONIC and its subsidiary improperly compensated surgeons and physicians in connection with the Infuse® device.

299. Senator Kohl's letter expressed several concerns, including the following:

> That account also addressed the corporate integrity agreement (CIA) that MEDTRONIC and its subsidiary entered into with the Office of the Inspector General of the United States Department of Health and Human Services stemming from those same allegations. In that same letter to the Committee, MEDTRONIC and its subsidiary both denied that "improper payments were made to physicians in the first place (MEDTRONIC's agreement with DOJ does not contain any admission of liability), much less that improper payments 'have continued.' Consequently, it was with

> concern that I read recent articles, in the *Wall Street Journal* and elsewhere, which outlined highly disturbing allegations of improper, if not illegal, payments by MEDTRONIC to surgeons and physicians.
>
> These continuing allegations are directly relevant to the Committee's oversight of inappropriate physician compensation practices within the medical device industry. All of the major orthopedic device companies that settled with DOJ over such allegations were required to publicly reveal information related to their payments to physicians. MEDTRONIC's response to the Committee's initial inquiry articulated no specific reasons as to why MEDTRONIC has yet to voluntarily make the same disclosures.

300. In this letter, Senator Kohl requested both documentation of MEDTRONIC's efforts to comply with the July 2006 Settlement Agreement and interviews with corporate witnesses and documents "given the ongoing, serious concerns publicly raised regarding the integrity and transparency of MEDTRONIC's physician compensation practices."

301. Senator Kohl also asked MEDTRONIC to explain "the circumstances that led MEDTRONIC's former counsel to file suit against the company [alleging improper payments to physicians] and how that matter was subsequently settled."

302. Also on September 30, 2008, U.S. Senator Charles Grassley sent a similar letter to MEDTRONIC pertaining to the marketing of Infuse® and allegations of related kickbacks to physicians regarding the sale of Infuse®, noting that:

> Last week, the *Wall Street Journal (WSJ)* reported on allegations of financial perks provided to doctors that included "entertainment at a Memphis strip club, trips to Alaska and patent royalties on inventions they played no part in."[119] I would appreciate your assistance in better understanding these allegations and would like to take this opportunity to lay out my specific concerns and questions.

303. Senator Grassley went on to express his concern over the *Wall Street Journal*'s reports "that one of the incentives MEDTRONIC provided physicians was to include them on patents for medical devices and reward them with royalties, even though the physicians may not have contributed to the development of the product."

[119] David Armstrong, "Lawsuit Says MEDTRONIC Gave Doctors Array of Perks," *Wall St. J.*, Sept. 25, 2008.

304. This letter specifically addressed issues related to MEDTRONIC's marketing of Infuse®:

> Fourth, earlier this month the WSJ reported on problems with off-label use of MEDTRONIC's Infuse®. Infuse® is a bone graft replacement technology that uses a protein which creates bone. Specifically, it was reported that MEDTRONIC gave payments to physicians, in the form of consulting agreements, as a means of increasing sales of Infuse®. The allegations that MEDTRONIC has been disguising these consulting agreements as inducements or kickbacks for physicians to use Infuse® are equally troubling. Likewise, this is a practice that I would like to better understand and I would like to know what if anything has changed since these reported events.

305. Senator Grassley, in his September 30, 2008 letter, also questioned why several lawsuits against MEDTRONIC pertaining to Infuse® remained under seal, and indicated that he would like to "better understand the status of these lawsuits and the procedural process that has led to the current situation."

ii) June 21, 2011 Letter.

306. The U.S. Senate Committee on Finance investigated whether MEDTRONIC has continued to misrepresent the adverse events that result from Infuse® and rhBMP-2, as well as the possibility that MEDTRONIC improperly influenced clinical trials and reporting regarding rhBMP-2.

307. On June 21, 2011, U.S. Senators Charles Grassley and Max Baucus sent another letter to MEDTRONIC on behalf of the Senate Committee on Finance requesting that MEDTRONIC produce documents and communications pertaining to "adverse postoperative events and/or medical complications" resulting from the use of rhBMP-2.[120] The letter also requests that MEDTRONIC provide "[a] detailed account of payments that MEDTRONIC made to all Infuse® clinical investigators."

308. In their June 21, 2011 letter, Senators Grassley and Baucus state: "We are extremely troubled by press reports suggesting that doctors conducting clinical trials examining

[120] Letter from Grassley and Baucus (June 21, 2011), *available at*, http://finance.senate.gov/newsroom/chairman/release.

the safety and effectiveness of Infuse® on behalf of MEDTRONIC were aware that Infuse®, a treatment commonly used in spinal surgery, may cause medical complications, but failed to report this in the medical literature. This issue is compounded by the fact that some clinical investigators have substantial financial ties to MEDTRONIC."

309. The letter further states: "We are also concerned that other severe side-effects of Infuse® and similar bone-growth products developed by MEDTRONIC may have been unreported or under-reported in clinical literature. Reports have linked Infuse® to potentially fatal swelling in the neck and throat, and radiating leg pain. Concerns have also been expressed about a potential link to cancer."

iii) **December 13, 2011 Letter**

310. Senators Herb Kohl, Charles Grassley, and Richard Blumenthal wrote to MEDTRONIC again in December 2011 demanding more information from the company over adverse events caused by on-label and off-label use of Infuse®. The letter noted that "your company has experienced safety issues, such as with your spine product Infuse®."

311. The letter also demanded that MEDTRONIC explain whether or not it requires physicians who receive funds from MEDTRONIC to disclose those payments to their patients before the patients receive one of MEDTRONIC's medical devices and "If not, why not?"

312. This new letter requires that MEDTRONIC produce this information to the U.S. Senate's Special Committee on Aging by no later than January 23, 2012.

313. On information and belief, this continued investigation by a U.S. Senate committee suggests that MEDTRONIC has not changed its ways with regard to its illegal promotion of Infuse®, despite signing the CIA and paying a $40 million fine to DOJ in 2006.

d) **Oregon Attorney General Investigation**

314. On March 13, 2012, the Oregon Attorney General's Office ("Oregon AG") issued an Investigative Demand pursuant to Ore. Rev. Stat. § 646.618 to MEDTRONIC targeting the sales, marketing, and promotional practices of MEDTRONIC and its Oregon sales

representatives to Oregon healthcare providers with respect to Infuse®, its adverse effects, and its off-label uses.

315. MEDTRONIC has resisted full compliance with the Oregon AG's Investigative Demand. For example, MEDTRONIC has only agreed to produce certain responsive documents pursuant to a Confidentiality Agreement.

316. Nevertheless, as part of the Oregon AG's investigation, MEDTRONIC has disclosed there were nearly 50 MEDTRONIC sales representatives in Oregon who provided information regarding Infuse® to Oregon healthcare providers. MEDTRONIC has also identified the Oregon physicians who were MEDTRONIC consultants for Infuse® from January 1, 2007 to the present, namely Leon Assael, Miroslav Bobek, Aleksander Curcin, Gerald Alan Harper, and Jay Malmquist.

317. The Oregon AG's investigation into MEDTRONIC's illegal and misleading promotional, sales, and marketing practices associated with Infuse®, its adverse effects, and its off-label uses is ongoing.

11) Allegations in Support of Punitive Damages

318. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further alleges as follows:

319. At all times herein referenced, officers, directors, and managing agents of MEDTRONIC knew, and were aware, and concealed, hid, and/or otherwise downplayed the true risks of non-FDA approved off-label uses of its product Infuse®.

320. At all times herein referenced, officers, directors, and managing agents of MEDTRONIC knew, and were aware, that numerous people had ectopic bone formation, radiculitis, osteolysis, cage migration, and worse overall outcomes as a result of non-FDA approved off-label uses of its product Infuse®.

321. The MEDTRONIC defendants designed, engineered, developed, manufactured, fabricated, assembled, equipped, tested or failed to test, inspected or failed to inspect, labeled, advertised, promoted, marketed, supplied, distributed, wholesaled, and sold Infuse®, a product

which said Defendants knew to be dangerous and unsafe for the purpose for which they intended it to be used, namely, as a bio-engineering bone draft device in spinal fusion surgeries.

322. At all times herein mentioned, prior to and at the time that Defendants designed, developed, manufactured, promoted, marketed, supplied, distributed, tested or failed to test, and/or sold Infuse® to Plaintiff LIGIA VANESSA CHAPETON and Plaintiff's physicians, and prior to the time that said product was used, MEDTROINC knew, or should have known, that Infuse® was defectively designed and manufactured, that it had extremely dangerous properties and defects, and that it had defects which would cause serious injuries and damage to users of said product, thereby threatening the life and health of the users. Further, at all times, all Defendants knew that Infuse® had caused serious injuries and damage to other members of the public.

323. At all times herein mentioned, all Defendants, despite the actual knowledge described hereinabove, intentionally suppressed the adverse events and other complaints and reports of injuries, actively concealed and downplayed the risks associated with Infuse®, actively promoted the off-label use of Infuse®, failed to warn Plaintiff and the medical community of the true risks associated with Infuse®, saturated the scientific and medical literature with biased, industry-funded studies to conceal the true risks of Infuse®, and otherwise failed to warn Plaintiff, the medical community, and/or the general public of the true risks of off-label use of Infuse®.

324. At all times herein mentioned, Defendants had actual knowledge of the facts hereinabove alleged demonstrating serious injury to patients in which Infuse® was implanted, particularly in an off-label manner such as without an LT-CAGE™ like the surgery Plaintiff underwent. Defendants nevertheless deliberately suppressed, concealed, downplayed, and/or otherwise hid any information demonstrating the true risks associated with Infuse® from Plaintiff, the medical community, and/or the general public. Instead, Defendants continued to actively promote the off-label use of Infuse® to spine surgeons in an effort to maintain and increase Infuse®'s enormous profitability.

325. As a legal and proximate result of Defendants' conduct, as herein alleged, Plaintiff sustained the injuries and damages set forth above.

326. Defendants' conduct and omissions, as set forth above, in allowing such an extremely dangerous product to be used by members of the general public, including Plaintiff, constitutes fraud, malice and oppression toward Plaintiff and others, and demonstrates a callous and conscious disregard of the safety of Plaintiff and others.

327. Plaintiffs are therefore entitled to exemplary or punitive damages, which would serve to punish the Defendants and to deter wrongful conduct in the future.

328. Plaintiffs are therefore entitled to judgment against Defendants as hereinafter set forth.

a) Infuse® is Profitable and thus MEDTRONIC had an Economic Motive to Promote Infuse Off-label.

329. Infuse® has become a best seller for MEDTRONIC. MEDTRONIC's Infuse® sales have exceeded $3.6 billion since the launch of the Infuse® Bone Graft in July 2002. As a J.P. Morgan research analyst covering MEDTRONIC noted in a report dated November 12, 2008:

> Infuse® is an $800M product for MEDTRONIC (6% of sales), having enjoyed robust growth since its initial approval in the U.S. in July 2002. In fact, it is the one piece of MEDTRONIC's Spine business that continues to post strong double-digit growth without any issues (LTM: +16.9%). That is, until now.

330. MEDTRONIC has depended heavily on Infuse® sales because so many of its other products, such as cardiac defibrillators, have slowed as the result of recalls of those defective defibrillators in the past several years.

331. Revenue generated by sales of Infuse® was approximately $800 million for the 2011 fiscal year, and the vast majority of these sales were attributable to off-label use of the product. Off-label uses of Infuse® account for 85% to 90% of all spine surgeries involving Infuse®.

332. Plaintiffs are informed and believes and based thereon alleges that, as a result of MEDTRONIC's illegal and improper off-label promotion, sales of Infuse® have soared and have totaled more than 4 billion of dollars from 2002 to 2011.

333. MEDTRONIC has consistently sought to expand the use of Infuse® by, among other things, illegally and improperly promoting dangerous and/or insufficiently studied off-label uses for Infuse® in various parts of the spine for various types of spine surgeries, as discussed throughout this Complaint.

b) June 1, 2011 Issue of *The Spine Journal.*

334. On June 1, 2011, the *Spine Journal*, a leading medical journal in the United States, published a special edition dedicated to addressing serious patient safety and ethical concerns related to the use of rhBMP-2 (Infuse®) in the spine.

335. This special edition reviewed thirteen peer-reviewed articles about rhBMP-2 by MEDTRONIC-sponsored authors, and concluded that these articles had inaccurately reported the safety of rhBMP-2 applications in the spine by underestimating its risks.

336. In an editorial summarizing the findings of this special issue, five prominent physicians, including spine surgeons at Stanford University Medical Center, wrote that the earlier industry-sponsored trials and reports were "remarkable for the complete absence of reported rhBMP-2-related clinical adverse events." For example, the industry-sponsored articles omitted mention of indications from the earliest trials of inflammatory reactions, adverse back and leg pain events, radiculitis, retrograde ejaculation, urinary retention, bone resorption, and implant displacement. They also omitted mention of sterility and cancer risks associated with rhBMP-2, as reported in FDA documents and hearings. The trials and reports suffered from idiosyncratic trial design, reporting bias, and peer-review/publication shortfalls.

337. According to this editorial and several of the accompanying articles in the *Spine Journal*, the thirteen MEDTRONIC-funded articles reported only successful fusions and extremely low or nonexistent rates of complications with Infuse®, which led to the growth of "off-label" use of Infuse® in lumbar fusion procedures. The articles "may have promoted

widespread poorly considered on- and off-label use, eventual life-threatening complications and deaths."

338. Contrary to the conclusions of the earlier MEDTRONIC-sponsored trials and articles, an article in this special issue of the *Spine Journal* suggested "an estimate of adverse events associated with rhBMP-2 use in spine fusion ranging from 10% to 50% depending on approach."

> Anterior cervical fusion with rhBMP-2 has an estimated 40% greater risk of adverse events with rhBMP-2 in the early postoperative period, including life-threatening events. After anterior interbody lumbar fusion rates of implant displacement, subsidence, infection, urogenital events, and retrograde ejaculation were higher after using rhBMP-2 than controls. *Posterior lumbar interbody fusion was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes.* In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to or greater than that of iliac crest bone graft harvesting, and 15% to 20% of subjects reported early back pain and leg pain adverse events; higher doses of rhBMP-2 were also associated with a greater apparent risk of new malignancy."

Eugene J. Carragee, Eric L. Hurwitz & Bradley K. Weiner, *A Critical Review Of Recombinant Human Bone Morphogenetic Protein-2 Trials In Spinal Surgery: Emerging Safety Concerns And Lessons Learned*, The Spine Journal 11, 471-72 (2011) (emphasis added).

339. This article also reported that ten of the earlier industry-sponsored rhBMP-2 trials were funded in whole or in part by the manufacturer of rhBMP-2 (Infuse®), MEDTRONIC. Furthermore, in twelve of these earlier studies, the median-known financial association between the authors and MEDTRONIC Inc. was approximately $12,000,000-$16,000,000 per study (range, $560,000-$23,500,000). *Id.* at 475.

340. The following are some of the other significant conclusions in these articles in the June 1, 2011 Issue of *The Spine Journal*:

a. Many of the risks now accepted have been known since a publication by Poynton and Lane in 2002, which listed overgrown and uncontrolled bone formation, osteoclast activity (graft subsidence, migration, loss of fixation etc.), local safety (inflammation, edema,

wound problems, and infection), potential negative effect of BMPs on exposed dura and nerves (neurologic events, retrograde ejaculation, persistent bladder retention, early back pain, leg pain, radiculitis, functional loss, carcinogenicity). *However, it appears that these risks were ultimately washed out and marginalized by the wealth of positive data from industry-sponsored studies.*

b. A 2-year rhBMP-2 follow-up published by Burkus, et al., reported no adverse events. However, in a 6-year follow-up publication using the same subjects, the authors contradict their earlier publication stating that there had been seven early adverse events associated with subsidence in the rhBMP-2 group, yet they were not reported in the two year follow-up.

c. In fact, on closer inspection of the Burkus studies, it was noted that all adverse events mentioned in the six-year follow-up had occurred within the first two years.

d. Furthermore, four of the adverse events required further surgery, and 22 additional surgeries for device failures occurred in the same rhBMP-2 group between 0-2 years after surgery according to the FDA summary, but were not specifically reported in the 2003 or 2004 studies, which were the same patients over the same time frame.

e. The estimates of rhBMP-2 safety from the original publications underestimated rhBMP-2-related adverse events of the product. In the small pilot studies, there were inadequate numbers to assess safety, but some suggestion of potential harm was seen in at least one study. In the larger trials, there is evidence in each trial that rhBMP-2 complications may be common and may be serious, but in each publication these were underreported.

f. The presence and magnitude of conflicts-of-interest and the potential for reporting bias were either not reported or were unclear in each of the original industry sponsored studies. Some of the conflicts-of-interest statements reported appeared to be vague, unintelligible, or were internally inconsistent.

g. The original estimates of ICBG (Iliac Crest Bone Graft, the pre-rhBMP-2 gold standard procedure for spinal fusion) harvesting morbidity were based on invalid

assumptions and methodology. This in turn may have exaggerated the benefit or underestimated the morbidity of rhBMP-2 in the clinical situations tested.

h. The control group methods and techniques, as selected for both posterior approach methods (PLIF and PLF) were potentially handicapped by significant design bias against the controls.

i. In those studies for which other data sources have been made available on the same patient sets (either FDA documents or subsequent reporting of follow-up data), serious contradictory findings have emerged. Major complications, additional surgeries, neurologic/urologic injury, and major back/leg pain events were apparently observed but not reported in the original articles.

j. By falsely reporting perfect or near perfect safety, the original studies might have led others to widespread off-label use of the product with some potentially catastrophic outcomes. Revised estimates of adverse events are:

i. Posterior lumbar interbody fusion techniques: 25-50% risk of associated adverse events.

ii. Anterior lumbar interbody fusion: 10-15% risk of adverse events.

iii. Anterior cervical fusion: 40% greater risk of adverse events in the acute postoperative period including potentially life-threatening complications.

iv. Posterolateral fusions: equivalent or greater early postoperative risk of morbidity compared with ICBG harvesting for this dosage; 16-20% of rhBMP-2 subjects had adverse back and leg pain events, *a probable two to threefold increase in the first three months after surgery over control groups* (emphasis added).

c) **October 25, 2012 U.S. Senate Committee on Finance Report**

341. On October 25, 2012, Senate Finance Committee released the results of its 16-month investigation into MEDTRONIC, which revealed questionable ties between the company and its physician "Opinion Leader" consultants tasked with testing and reviewing Infuse®. Ex.

C, Senate Finance Committee Report.[121] Without public disclosure of their roles, MEDTRONIC employees collaborated with the physician authors to edit – and in some cases, write – segments of published studies on Infuse®. The studies may have inaccurately represented Infuse®'s risks and may have overemphasized the side effects of prior more traditional treatments. The Senate report found that MEDTRONIC also maintained significant, previously-undisclosed financial ties with the physicians who authored the early studies on Infuse®, making $210 million in payments to physicians over a 15-year period.

342. The major findings of the investigation include:

a. MEDTRONIC was involved in drafting, editing, and shaping the content of medical journal articles on Infuse® authored by its physician consultants who received significant amounts of money through royalties and consulting fees from MEDTRONIC. The company's significant role in authoring or substantively editing these articles was not disclosed in the published articles. Medical journals should ensure any industry role in drafting articles or contributions to authors be fully disclosed.

b. MEDTRONIC paid a total of approximately $210 million to physician authors of MEDTRONIC-sponsored studies from November 1996 through December 2010 for consulting, royalty and other arrangements.

c. An e-mail exchange shows that a MEDTRONIC employee recommended against publishing a complete list of adverse events, or side effects, possibly associated with Infuse® in a 2005 *Journal of Bone and Joint Surgery* article.

d. MEDTRONIC officials inserted language into studies that promoted Infuse® as a better technique than an alternative by emphasizing the pain associated with the alternative.[122]

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[121] The Senate's full report is available online at: http://www.finance.senate.gov/newsroom/chairman/download/?id=e54db17c-a475-4948-bd81-69c8740c6aaf. In the interest of brevity, Plaintiff has not attached the full 2,315 page report.
[122] *Id.* at 2.

12) Plaintiff-specific Allegations

343. On June 9, 2011, Plaintiff LIGIA VANESSA CHAPETON was implanted with Infuse® in a spinal fusion via a posterior implantation method at the L5-S1 levels by Dr. Roger Hartl ("Dr. Hartl") at New York Presbyterian Hospital-Cornell in New York, New York County. The use of Infuse® was off-label in this surgery because (1) it was implanted by means of a posterior approach, and (2) the requisite LT-Cage™ was not used; a PEEK cage was used.

344. Prior to this surgery, MEDTRONIC did not inform Plaintiff LIGIA VANESSA CHAPETON that there were any risks specific to the off-label use of Infuse® in the lumbar spine, and MEDTRONIC did not adequately inform her implanting surgeon, Dr. HARTL, of the true incidence of ectopic, uncontrolled, or unusual bone growth resulting from the use of Infuse® in off-label procedures, or of other risks, dangers, or complications associated with the off-label use of Infuse® in the spine.

345. Following her June 2011 Infuse® surgery, Plaintiff LIGIA VANESSA CHAPETON developed bilateral radiculopathy and chronic lower back pain which progressively got worse. Imaging studies ultimately showed that Plaintiff LIGIA VANESSA CHAPETON had developed uncontrolled bone growth (aka "bone overgrowth") or heterotopic ossification causing severe nerve impingement, osteolysis, stenosis, and cystic changes at or near the site of the June 2011 surgery.

346. On June 25, 2013, Plaintiff LIGIA VANESSA CHAPETON underwent a revision surgery at New York Downtown Hospital in New York, New York County performed by Paul Brisson, M.D., to remove the existing hardware and to re-do the failed fusion. Upon revision, there was evidence of "recess stenosis secondary to bone formation within neural canal, left L5-S1..., which Dr. Bisson noted was "clearly a mass effect caused by the heterotropic bone..."

347. As a direct and proximate result of the off-label use of Infuse®, Plaintiff LIGIA VANESSA CHAPETON now suffers from severe injuries and damages as described herein. Plaintiff LIGIA VANESSA CHAPETON experiences bilateral chronic pain in her legs, feet, and toes.

348. MEDTRONIC's fraudulent concealment of the relevant facts tolled any relevant statutes of limitation.

349. As a result of the off-label use and failure to warn of the risks of off-label use of Infuse® as manufactured, sold and supplied by MEDTRONIC, and as a result of the negligence, callousness and the other wrongdoing and misconduct of MEDTRONIC, as described herein:

350. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

351. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

352. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

353. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

354. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

355. Defendants' conduct as alleged above was malicious, intentional and outrageous and constitutes a willful and wanton disregard for the rights and safety of others. Such conduct was directed specifically at Plaintiffs and as such, warrants an imposition of punitive damages.

CLAIMS FOR RELIEF

FIRST CAUSE OF ACTION
Fraudulent Misrepresentation and Fraud in the Inducement
(By Plaintiff LIGIA VANESSA CHAPETON against the MEDTRONIC Defendants)

356. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further allege as follows:

357. In connection with their Infuse® products, MEDTRONIC fraudulently and intentionally misrepresented material and important health and safety product risk information

from Plaintiffs and Plaintiff LIGIA VANESSA CHAPETON's physicians; all as alleged in this Complaint. Plaintiff and Plaintiff's physicians would not have decided to use Infuse® without an LT-Cage™ or to implant it via posterior or lateral approaches had they known of the safety risks related to Infuse®.

358. Plaintiffs make the following specific fraud allegations with as much specificity and particularity as possible absent access to the information necessarily available only to the MEDTRONIC Defendants:

a. **Who**: Defendants Medtronic, Inc. and Medtronic Sofamor Danek, USA, Inc.

b. **What**: Medtronic expressly misrepresented the risks and dangers associated with the use of Infuse® in spinal surgeries by, *inter alia*, downplaying the risk of bone overgrowth, concealing adverse events resulting from the use of Infuse® in spinal fusion surgeries and over-emphasizing problems associated with non-Infuse® bone graft products used in spine fusion procedures. *See* ¶¶ 170-212.

c. **When**: Since the FDA's July 2, 2002 PMA approval of the Infuse® combination device. *See* ¶ 221.

d. **Where**: Medtronic made these misrepresentations in a series of published studies funded by the Company, thirteen of which were specifically challenged in an article authored by Eugene J. Carragee, MD, entitled *A Critical Review of Recombinant Human Bone Morphogentic Protein-2 Trials in Spinal Surgery: Emerging Safety Concerns and Lessons Learned*. *See* ¶ 170, 335. The thirteen studies include a 2004 article released in *The Spine Journal*, entitled *Posterior lumbar interbody fusion using recombinant human bone morphogenic protein type 2 with cylindrical interbody cages*, authored by Regis W. Haid, MD, Charles L. Branch, Jr., MD, Joseph T. Alexander, MD and J. Kenneth Burkus, MD. *See* ¶¶ 133, 161, 171-3. This article downplayed the risk of bone overgrowth and was edited by a Medtronic employee to include comments supportive of the use of Infuse® in an off-label posterior approach. *See* ¶¶ 134, 211, 233, 248, 270, 296. Such studies and their findings were touted to physicians at

presentations and conferences nationwide by surgeon "Opinion Leaders," and promoted by Medtronic sales representatives directly to surgeons. *See* ¶¶ 130-62.

e. **How**: Medtronic systematically manipulated the medical literature regarding Infuse® by paying substantial sums of money to surgeon Opinion Leaders who authored articles that reported favorably the benefits of using Infuse® in spinal fusion surgeries, while concealing and downplaying known dangers and risks. *See* ¶ 132-4. In addition, Medtronic employees ghostwrote and edited various publications and peer-reviewed responses to those publications. *See* ¶ 170, 174, 220. Medtronic withheld information about its financial ties to the studies' authors and their involvement in the editing and writing process. In turn, the Opinion Leaders touted the studies and their findings at presentations and conferences nationwide, Medtronic sales representatives steered surgeons to these Opinion Leaders and their writings, and Medtronic employees directly promoted off-label uses of Infuse®. *See* ¶¶ 130-62 (identifying and describing Opinion Leader activities), 108.

Several spine surgeons have already testified under oath at depositions that MEDTRONIC sales personnel overtly and directly promoted to them the off-label use of Infuse® in the spine. *See* ¶ 271. A surgeon in another case involving Infuse® has also testified that a MEDTRONIC representative told him that the risk of bone overgrowth was not a cause for concern in his patient. *See* ¶ 218.

f. **Why**: Medtronic manipulated the medical literature regarding Infuse® to promote off-label uses of Infuse® to boost its sales of the product. *See* ¶¶ 269-72, 323-4. Plaintiffs have also alleged that during the years following the PMA approval of the Infuse® combination device, as Medtronic carried out its off-label promotion activities, use of genetically modified bone growth protein increased more than four times, spinal fusion surgeries accounted for more than ninety percent of these procedures, and the vast majority of the spinal fusion surgeries involved off-label uses of the bone protein. *See* ¶ 250.

359. Plaintiff and Plaintiff's physicians were justified in relying, and did rely, on MEDTRONIC's concealment of information and misrepresentations about the safety risks

related to Infuse® in deciding to make use of Infuse® in an off-label manner in Plaintiff's lumbar spine fusion surgery.

360. As the direct, proximate and legal result of Defendants' fraudulent concealment and misrepresentations and suppression of material health and safety risks relating to Infuse® and Defendants' dangerous and irresponsible marketing and promotion practices, Plaintiffs have been injured and have incurred damages including, but not limited to, medical and hospital expenses, lost earning capacity, physical and mental pain and suffering, loss of the enjoyment of life and loss of consortium.

361. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

362. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

363. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

364. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

365. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

366. Defendants' conduct as alleged above was malicious, intentional and outrageous and constitutes a willful and wanton disregard for the rights and safety of others. Such conduct was directed specifically at Plaintiffs and as such, warrants an imposition of punitive damages.

SECOND CAUSE OF ACTION
Strict Products Liability – Failure To Warn
(By Plaintiff LIGIA VANESSA CHAPETON against the MEDTRONIC Defendants)

367. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further allege as follows:

368. MEDTRONIC had a duty to warn Plaintiff and Plaintiff's physicians about the dangers of Infuse® of which it knew, or in the exercise of ordinary care, should have known, at the time the Infuse® left Medtronic's custody or control.

369. MEDTRONIC did know of these dangers of off-label use of Infuse®, and breached this duty by failing to warn Plaintiff and Plaintiff's physicians of the dangers of its off-label practice of using Infuse® without an LT-Cage™ and placing it posteriorly or laterally in a lumbar spine fusion surgery.

370. Defendants, and each of them, knew that Infuse® would be purchased and used without inspection for defects in the design of the product.

371. The Infuse® used in Plaintiff was defective when it left the control of each of these Defendants.

372. Defendants knew or should have known of the substantial dangers involved in the reasonably foreseeable use of Infuse®, whose defective design, manufacturing, and lack of sufficient warnings caused Infuse® to have an unreasonably dangerous propensity to cause catastrophic injuries.

373. The warnings accompanying the Infuse® product did not adequately warn Plaintiff and Plaintiff's physicians, in light of the scientific and medical knowledge at the time, of the dangers associated with Infuse® when used without an LT-Cage™ and when placed posteriorly or laterally in a lumbar spine fusion surgery including, but not limited to, pain and weakness in limbs, radiculitis, ectopic bone formation, osteolysis, and worse global outcomes than alternative, currently available treatments.

374. The warnings accompanying the Infuse® product failed to provide the level of information that an ordinary physician or consumer would expect when using the product in a manner reasonably foreseeable to MEDTRONIC. MEDTRONIC either recklessly or intentionally minimized and/or downplayed the risks of serious side effects related to the off-label use of Infuse®, including, but not limited to, the risk of ectopic or uncontrolled bone growth.

375. MEDTRONIC failed to provide adequate warnings, instructions, guidelines or admonitions to members of the consuming public, including Plaintiff and Plaintiff's physicians, of the problems with off-label use of Infuse®, which Defendants knew, or in the exercise of reasonable care should have known, to have existed with the off-label use of Infuse®.

376. Defendants knew that these substantial dangers are not readily recognizable to an ordinary consumer or physicians, and that consumers and physicians would purchase Infuse® without inspection.

377. At the time of Plaintiff's injury, Infuse® was being used in a manner promoted by Defendants, and in a manner that was reasonably foreseeable by Defendants as involving substantial danger that was not readily apparent to its users.

378. Plaintiff's physician relied on MEDTRONIC's inadequate warnings and omissions in deciding to use Infuse® in an off-label manner. Plaintiff and Plaintiff's physician would not have made off-label use of Infuse® without an LT-Cage™ and placement of it posteriorly or laterally had they known of the true safety risks related to Infuse®.

379. As a direct and proximate result of one or more of the above-listed dangerous conditions and defects, and of MEDTRONIC's failure to provide adequate warnings about them, Plaintiffs sustained serious injuries of a personal and pecuniary nature from approximately June 2011 to the present.

380. Plaintiff LIGIA VANESSA CHAPETON has sustained extreme pain, suffering, and anguish from the date of Plaintiff's lumbar spine fusion surgery in which Infuse® was implanted without an LT-Cage™ and was placed posteriorly until the present.

381. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

382. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

383. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

384. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

385. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

386. Defendants' conduct as alleged above was malicious, intentional and outrageous and constitutes a willful and wanton disregard for the rights and safety of others. Such conduct was directed specifically at Plaintiffs and as such, warrants an imposition of punitive damages.

THIRD CAUSE OF ACTION
Strict Products Liability – Design Defect
(By Plaintiff LIGIA VANESSA CHAPETON against the MEDTRONIC Defendants)

387. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further alleges as follows:

388. Defendants' Infuse® device was defectively designed at the time that it left the Defendants' control and was placed into the stream of commerce in New York. The device reached Plaintiff without a substantial change in the condition in which it was sold.

389. Defendants' Infuse® device was defectively designed because it was designed for sale without the LT-CAGE™ and, by promoting and selling it as such, MEDTRONIC has unlawfully designed, manufactured, marketed and sold a new device for which the FDA never weighed the risk versus the benefit and never approved. Moreover, this new device presents risks and dangers that render it defective.

390. Defendants' Infuse® device was defectively designed because the design was unsafe when used in the manner promoted by Defendants and/or in a manner reasonably foreseeable by Defendants. The Infuse® product failed to perform as safely as an ordinary

consumer would expect when used, as it was promoted by MEDTRONIC for use off-label without an LT-Cage™® and placement posteriorly or laterally in lumbar spine fusion surgeries.

391. Defendants' Infuse® device was defectively designed because the risks of danger in the design outweigh the benefits of the design.

392. The Infuse® product was designed in a way that caused users to suffer injuries including, but not limited to, pain and weakness in limbs, radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes than equally-effective, alternative designs and treatments.

393. The foreseeable risks of harm posed by using the Infuse® product in a manner promoted by Defendants could have been reduced or avoided by adopting a reasonable alternative design. Defendants did not adopt a design that would have rendered the Infuse® product reasonably safe.

394. Plaintiff and Plaintiff's physicians used Infuse® in a manner intended and reasonably foreseeable by Defendants.

395. Plaintiff was not aware of the aforementioned defects at any time prior to the injuries caused by the Infuse®.

396. As a legal and proximate result of the aforementioned defects of Infuse®, Plaintiff has sustained the injuries and damages set forth herein.

397. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

398. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

399. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

400. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

401. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

402. Defendants' conduct as alleged above was malicious, intentional and outrageous and constitutes a willful and wanton disregard for the rights and safety of others. Such conduct was directed specifically at Plaintiffs and as such, warrants an imposition of punitive damages.

FOURTH CAUSE OF ACTION
Strict Product Liability – Misrepresentation
(By Plaintiff LIGIA VANESSA CHAPETON against the MEDTRONIC Defendants)

403. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further allege as follows:

404. Specific defects in the Infuse® product, as specified above in this Complaint, rendered it defective and unreasonably dangerous.

405. At all relevant times, Defendants were engaged in the business of selling Infuse® for resale or use, and in fact did sell the Infuse® device used by Plaintiff's implanting surgeon. In the course of marketing Infuse®, MEDTRONIC made untrue representations of material facts and omitted material information to Plaintiff, Plaintiff's physicians, and the public at large. MEDTRONIC sponsored biased medical trials, reports, and articles that wrongfully and inaccurately claimed that the dangers inherent to off-label use of Infuse® did not exist or were significantly less than the actual dangers. MEDTRONIC made these misrepresentations and omissions to guide physicians in their purchase and use of Infuse®.

406. Plaintiff and Plaintiff's physicians would not have purchased and made off-label use of Infuse® without an LT-Cage™ and placement of Infuse® posteriorly or laterally for a lumbar spine fusion surgery had they known of the true safety risks related to Infuse®.

407. Defendants were negligent in making the untrue misrepresentations and omitting material information because Defendants knew, or had reason to know, of the actual, unreasonable dangers and defects in their Infuse® product.

408. Plaintiff and Plaintiff's physicians would reasonably be expected to use Infuse®. Defendants intended to induce Plaintiff and Plaintiff's physicians to rely on their misrepresentations and omissions to use Infuse® in an off-label manner.

409. Plaintiff and Plaintiff's physicians were justified in relying, and did rely, on the misrepresentations and omissions about the safety risks related to Infuse® in deciding to make off-label use of Infuse® without an LT-Cage™ and placement of Infuse® posteriorly or laterally for a lumbar spine fusion surgery.

410. As the direct, producing, proximate and legal result of the Defendants' misrepresentations, Plaintiff has suffered severe physical pain, medical and hospital expenses, lost wages, pain and suffering, and pecuniary loss.

411. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

412. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

413. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

414. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

415. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

416. Defendants' conduct as alleged above was malicious, intentional and outrageous and constitutes a willful and wanton disregard for the rights and safety of others. Such conduct was directed specifically at Plaintiffs and as such, warrants an imposition of punitive damages.

FIFTH CAUSE OF ACTION
Product Liability – Negligence
(By Plaintiff LIGIA VANESSA CHAPETON against the MEDTRONIC Defendants)

417. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further allege as follows:

418. MEDTRONIC marketed its Infuse® product to and for the benefit of Plaintiff, and additionally marketed it to Plaintiff's physicians. Defendants knew or should have known that Plaintiff and Plaintiff's physicians would use the product, including for the off-label use of Infuse® without an LT-Cage™ and the placement of Infuse® posteriorly or laterally in lumbar spine fusion.

419. Defendants owed Plaintiff and Plaintiff's physician duties to exercise reasonable or ordinary care under the circumstances in light of the generally recognized and prevailing best scientific knowledge.

420. Defendants had a confidential and special relationship with Plaintiff due to (a) Defendants' vastly superior knowledge of the health and safety risks relating to Infuse®, and (b) Defendants' sole and/or superior knowledge of their dangerous and irresponsible practices of improperly promoting to physicians the off-label use of Infuse® without an LT-Cage™ and the placement of Infuse® posteriorly or laterally in lumbar spine surgeries.

421. As a result, Defendants had an affirmative duty to fully and adequately warn Plaintiff and Plaintiff's physicians of the true health and safety risks related to the off-label use of Infuse®, and Defendants had a duty to disclose their dangerous and irresponsible practices of improperly promoting to physicians the off-label use of Infuse® without an LT-Cage™ and the placement of Infuse® posteriorly or laterally for lumbar spine surgeries. Independent of any special relationship of confidence or trust, Defendants had a duty not to conceal the dangers of the off-label use of Infuse® to Plaintiff and Plaintiff's physicians.

422. Misrepresentations made by Defendants about the health and safety of Infuse® independently imposed a duty upon Defendants to fully and accurately disclose to Plaintiff and

Plaintiff's physicians the true health and safety risks related to Infuse®, and a duty to disclose their dangerous and irresponsible off-label promotion and marketing practices.

423. Through the conduct described in the foregoing and subsequent paragraphs of this Complaint, Defendants breached their duties to Plaintiff and to Plaintiff's physicians.

424. The following sub-paragraphs summarize, inter alia, Defendants' breaches of duties to Plaintiff and Plaintiff's physicians and describe categories of acts or omissions constituting breaches of duty by these Defendants. Each and/or any of these acts or omissions establishes an independent basis for these Defendants' liability in negligence:

a. Unreasonable and improper promotion and marketing of Infuse® to physicians, including but not limited to the promotion and marketing of Infuse® for off-label use without an LT-Cage™ in lumbar spine fusion surgeries;

b. Failure to warn physicians and Plaintiff of the dangers associated with Infuse® when used off-label without an LT-Cage™ and placed posteriorly or laterally in lumbar spine surgery including, but not limited to, pain and weakness in limbs, radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes than alternative treatments;

c. Failure to exercise reasonable care by not complying with federal law and regulations applicable to the sale and marketing of Infuse®; and

d. Failure to exercise reasonable care to prevent Infuse® from creating an unreasonable risk of harm to Plaintiff and other consumers who might reasonably be expected to be harmed by Infuse® while it was being used in the manner MEDTRONIC should have reasonably expected.

425. Defendants knew, or should have known, that, due to their failure to use reasonable care, Plaintiff and Plaintiff's physicians would use and did use Infuse®, to the detriment of Plaintiff's health, safety and well-being.

426. As the direct, producing, proximate and legal result of the Defendants' misrepresentations, Plaintiff has suffered severe physical pain, medical and hospital expenses, lost wages, pain and suffering, and pecuniary loss.

427. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

428. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

429. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

430. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

431. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

432. Defendants' conduct as alleged above was malicious, intentional and outrageous and constitutes a willful and wanton disregard for the rights and safety of others. Such conduct was directed specifically at Plaintiffs and as such, warrants an imposition of punitive damages.

SIXTH CAUSE OF ACTION
Breach of Express Warranty
(By Plaintiff LIGIA VANESSA CHAPETON against the MEDTRONIC Defendants)

433. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further alleges as follows:

434. At all times herein mentioned, the MEDTRONIC Defendants utilized journal articles, advertising media, sales representatives/consultants and paid Key Opinion Leaders to urge the use, purchase, and utilization of the off-label use of Infuse® and expressly warranted to physicians and other members of the general public and medical community Infuse® including uses in lumbar fusion procedures, was safe and effective for the off-label uses promoted by the MEDTRONIC Defendants

435. In doing so, on information and belief, MEDTRONIC made specific misrepresentations to Dr. Hartl and, likely other physicians, involved in caring for PLAINTIFF LIGIA VANESSA CHAPETON.

436. Defendants knew or, in the exercise of reasonable diligence, should have known that such off-label uses had the serious side effects set forth earlier in this Complaint .

437. Plaintiff is informed and believes and based thereon alleges that her treating surgeon relied on Defendants' express warranty representations regarding the safety and efficacy of off-label use of Infuse®, but such off-label uses, including uses in lumbar fusion procedures, were not effective, safe, and proper for the use as warranted in that Infuse® was dangerous when put to these promoted uses.

438. Defendants thus breached their express warranty which was a direct and proximate cause of Plaintiff's injuries and damages.

439. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

440. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

441. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

442. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

443. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

444. Defendants' conduct as alleged above was malicious, intentional and outrageous and constitutes a willful and wanton disregard for the rights and safety of others. Such conduct was directed specifically at Plaintiffs and as such, warrants an imposition of punitive damages.

SEVENTH CAUSE OF ACTION
Breach of Implied Warranties of Merchantability and Fitness
(By Plaintiff LIGIA VANESSA CHAPETON against the MEDTRONIC Defendants)

445. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further alleges as follows:

446. At all times herein mentioned, the MEDTRONIC Defendants utilized journal articles, advertising media, sales representatives/consultants and paid Key Opinion Leaders to urge the use, purchase, and utilization of the off-label use of Infuse® and impliedly warranted to physicians and other members of the general public and medical community that Infuse® was merchantable, fit, and safe for the off-label uses promoted by the MEDTRONIC Defendants.

447. In doing so, on information and belief, MEDTRONIC made specific misrepresentations to Dr. Hartl and, likely other physicians, involved in caring for PLAINTIFF LIGIA VANESSA CHAPETON.

448. The MEDTRONIC Defendants further impliedly warranted that Infuse®, which Defendants designed, manufactured, assembled, promoted and sold to Plaintiff LIGIA VANESSA CHAPETON and her physicians, was fit for the particular purposes for which the MEDTRONIC Defendants intended and promoted, namely off-label uses.

449. Contrary to these implied warranties, Infuse® was defectively designed, unmerchantable, and unfit for the new and unapproved off-label uses intended and promoted by the MEDTRONIC Defendants.

450. Defendants knew or, in the exercise of reasonable diligence, should have known that such off-label uses had the serious side effects set forth earlier in this Complaint.

451. Plaintiff is informed and believes and based thereon alleges that her treating surgeon relied on Defendants' implied warranty representations regarding off-label use of Infuse®, but such off-label uses, including uses in lumbar fusion procedures, were not effective, safe, and proper for the use as warranted in that Infuse® was dangerous when put to these promoted uses.

452. Defendants thus breached their implied warranty which was a direct and proximate cause of Plaintiff's injuries and damages.

453. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

454. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

455. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

456. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

457. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

458. Defendants' conduct as alleged above was malicious, intentional and outrageous and constitutes a willful and wanton disregard for the rights and safety of others. Such conduct was directed specifically at Plaintiffs and as such, warrants an imposition of punitive damages.

EIGHTH CAUSE OF ACTION
Loss of Consortium
(By Plaintiff GARY SEYMOUR against All Defendants)

459. Plaintiff GARY SEYMOUR incorporates by reference all previous paragraphs of this Complaint as if fully set forth here and further alleges as follows:

460. Plaintiff GARY SEYMOUR was at all relevant times the lawful spouse of Plaintiff LIGIA VANESSA CHAPETON.

461. As a further legal and proximate result of the wrongful conduct and negligence of all Defendants, Plaintiff GARY SEYMOUR has suffered and continues to suffer the loss of the services, society, and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON, as a result of her injuries caused by the Defendants' misconduct.

462. Plaintiff GARY SEYMOUR is therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

NINTH CAUSE OF ACTION
Medical Negligence
(By Plaintiff LIGIA VANESSA CHAPETON against Dr. HARTL)

463. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further allege as follows:

464. Plaintiff LIGIA VANESSA CHAPETON and Dr. HARTL had a patient-physician relationship at all times relevant to this Complaint.

465. Dr. HARTL was negligent in providing and performing medical services to Plaintiff as set forth in this Complaint.

466. The negligence of Dr. HARTL includes, but is not limited to, the following:

a. Performing a medically unnecessary spinal fusion surgery when less risky procedures such as a laminectomy and discectomy were more available and more appropriately indicated for Plaintiff LIGIA VANESSA CHAPETON;

b. Failure to inform Plaintiff of the true dangers and risks specific to the use of Infuse®;

c. Failure to inform Plaintiff of the fact that her spine surgery would involve the off-label and experimental use of Infuse®;

d. Failure to provide medical services in a professional and competent manner and otherwise comply with applicable standard of care;

e. Failure to conform to the standard of care ordinarily possessed and exercised by members of the same school of medicine practiced by Dr. HARTL;

f. Failure to use the same judgment and precautions that a reasonably prudent physician specializing in spine surgery would use;

g. Failure to appropriately treat Plaintiff's condition;

h. Failure to recognize Plaintiff's condition and making unwise and unprofessional choices for her case which fell below the applicable standard of care;

i. Failure to possess or use the same degree of knowledge, skill and care possessed and used by other physicians who would be providing medical services that were provided by this Defendant.

467. As a direct and proximate result of the negligence of Dr. HARTL, Plaintiff has incurred both economic losses and grievous non-economic injuries and losses, including severe pain and suffering as well as other limitations, chronic pain, physical discomfort, inconvenience, and loss of enjoyment and quality of life.

468. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

469. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

470. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

471. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

472. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

TENTH CAUSE OF ACTION
Failure to Obtain Informed Consent
(By Plaintiff LIGIA VANESSA CHAPETON against Dr. HARTL)

473. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further allege as follows:

474. Dr. HARTL fraudulently concealed from Plaintiff LIGIA VANESSA CHAPETON that Infuse® would be used in her spine fusion and it would be used in an off-label or experimental manner that was not approved by the FDA.

475. Dr. HARTL fraudulently concealed from Plaintiff LIGIA VANESSA CHAPETON of the risks inherent in off-label uses of Infuse®, including but not limited to ectopic bone growth.

476. The risks of off-label use of Infuse® were substantial. If fully informed of the common dangers and risks associated with off-label uses of Infuse®, a reasonable person, including Plaintiff, would not consent to such a procedure, or any decision to consent would be affected by such information.

477. A reasonably prudent spine surgeon practicing in the same community as Dr. HARTL would have fully informed a patient of an intended off-label use of Infuse®, and would have fully informed the patient of the risks inherent to such off-label use. Dr. HARTL's nondisclosure of this intended off-label use and the related dangers did not conform to, and fell below the medical community's standard of care.

478. At the time of Plaintiff's spinal fusion, Plaintiff was not informed of any intention to use Infuse® off-label, or of the potential risks involved with such use. To the extent that Plaintiff was informed of the intended use and any related dangers at the time he consented, DR. HARTL's disclosure was incomplete and inadequate.

479. DR. HARTL's failure to obtain Plaintiff's informed consent for the off-label use of Infuse®, and failure to obtain Plaintiff's informed consent concerning the inherent dangers and risks of Infuse®, constitutes a breach of the standard of care.

480. As a direct and proximate result of DR. HARTL's failure to obtain informed consent, Plaintiff has incurred both economic loss and grievous non-economic injuries and losses, including severe pain and suffering as well as other limitations, chronic pain, physical discomfort, inconvenience, and loss of enjoyment and quality of life.

481. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

482. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

483. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

484. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

485. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

ELEVENTH CAUSE OF ACTION
Fraudulent Misrepresentation and Fraud in the Inducement
(By Plaintiff LIGIA VANESSA CHAPETON against Dr. HARTL)

486. Plaintiffs incorporate by reference all previous and subsequent paragraphs of this Complaint as if fully set forth here and further allege as follows:

487. As her physician, Dr. HARTL had a duty to disclose to his patient, Plaintiff LIGIA VANESSA CHAPETON, the off-label use of Infuse® in her fusion surgery and the risks, dangers, and complications associated with the off-label use of Infuse® including the incidence of ectopic or uncontrolled or unusual bone growth.

488. Dr. HARTL fraudulently concealed from and misrepresented to Plaintiff LIGIA VANESSA CHAPETON the off-label use of Infuse® in her fusion surgery and the risks, dangers, and complications associated with the off-label use of Infuse® including the incidence of ectopic or uncontrolled or unusual bone growth.

489. Dr. HARTL knew that Plaintiff would regard the matters concealed and misrepresented to be important and material in determining whether to undergo a spinal fusion.

490. Dr. HARTL intended to cause Plaintiff to rely on his concealment of information and misrepresentations about the safety risks related to Infuse® to induce him to consent to its off-label use.

491. Plaintiff was justified in relying, and did rely, on Dr. HARTL's concealment of information and misrepresentations about the safety risks related to Infuse® in deciding to undergo a spinal fusion.

492. Dr. HARTL's concealment of the off-label use of Infuse® and the serious patient safety risks associated with off-label Infuse® were significant causes or contributing factors to the injuries sustained by his patient, LIGIA VANESSA CHAPETON.

493. As the direct, proximate and legal cause and result of Dr. HARTL's fraudulent concealment and misrepresentations and suppression of material health and safety risks relating to Infuse® Plaintiffs have been injured and have incurred damages including, but not limited to, medical and hospital expenses, lost wages and lost earning capacity, physical and mental pain and suffering, loss of the enjoyment of life and loss of consortium.

494. Plaintiff LIGIA VANESSA CHAPETON has been injured and suffers injuries to her body and mind, the exact nature of which are not completely known to date.

495. Plaintiff LIGIA VANESSA CHAPETON has sustained economic losses, including the loss of earning capacity, the exact amount of which is presently unknown.

496. Plaintiff LIGIA VANESSA CHAPETON will be required to incur additional medical expenses in the future to care for herself as a result of the injury and damages she has suffered.

497. Plaintiff GARY SEYMOUR has lost the society, comfort and consortium of his beloved wife, Plaintiff LIGIA VANESSA CHAPETON.

498. Plaintiffs are therefore entitled to damages in an amount to be proven at trial, together with interest thereon and costs.

TWELFTH CAUSE OF ACTION
Joint and Several Liability
(By Plaintiffs LIGIA VANESSA CHAPETON and GARY SEYMOUR against All Defendants)

499. The acts and omissions of all Defendants combined to cause injuries to Plaintiffs. As such, Defendants are jointly and severally liable to Plaintiffs.

500. All Defendants are vicariously liable to the Plaintiffs for the negligent acts of their employees and agents under the doctrine of respondeat superior.

501. All Defendants are liable to the Plaintiffs for the negligent acts of their apparent or ostensible agents.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs demand judgment against the Defendants, and each of them, in an amount which exceeds the jurisdictional limits of all lower courts, together with interests, costs, and disbursements of this action, including damages including, but not limited to:

1. Compensatory damages in excess of the jurisdictional amount of this Court, in an amount to be proven at trial;

2. Exemplary damages to be proven at trial;

3. Incidental, hospital and medical expenses according to proof;

4. Punitive damages for the reckless disregard of Plaintiffs' rights and gross negligence;

5. Attorneys' fees and costs; and

6. Other and further relief as this Court may deem just and proper.

Dated: January 21, 2014

Respectfully submitted,

LIEFF, CABRASER, HEIMANN & BERNSTEIN, LLP

By: */s Wendy R. Fleishman*
Wendy R. Fleishman

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Attorneys for Plaintiffs
Ligia Vanessa Chapeton and Gary Seymore

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF NEW YORK

LIGIA VANESSA CHAPETON, an individual, and GARY SEYMOUR, an individual

Plaintiffs,

-against-

MEDTRONIC, INC., a Minnesota corporation; MEDTRONIC SOFAMOR DANEK, USA, INC., a Tennessee corporation; ROGER HARTL, M.D., an individual

Defendants.

Date Filed:

INDEX No. 161291/2013

AFFIRMATION OF LIGIA VANESSA CHAPETON TO VERIFY THE COMPLAINT

I, Ligia Vanessa Chapeton, hereby affirm as true under all the penalties of perjury that I am a plaintiff in this action; that I have read the foregoing Complaint and know the contents thereof; that the same is true to my own knowledge, except as to the matters therein stated to be alleged on information and belief, and that those matters I believe to be true.

New York, New York

Dated: January 17, 2014

LIGIA VANESSA CHAPETON

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF NEW YORK

LIGIA VANESSA CHAPETON, an individual, and GARY SEYMOUR, an individual

Plaintiffs,

-against-

MEDTRONIC, INC., a Minnesota corporation; MEDTRONIC SOFAMOR DANEK, USA, INC., a Tennessee corporation; ROGER HARTL, M.D., an individual

Defendants.

Date Filed:

INDEX No. 161291/2013

AFFIRMATION OF GARY SEYMOUR TO VERIFY THE COMPLAINT

I, Gary Seymour, hereby affirm as true under all the penalties of perjury that I am a plaintiff in this action; that I have read the foregoing Complaint and know the contents thereof; that the same is true to my own knowledge, except as to the matters therein stated to be alleged on information and belief, and that those matters I believe to be true.

New York, New York

GARY SEYMOUR

Dated: January 17, 2014

FILED: NEW YORK COUNTY CLERK 01/21/2014 INDEX NO. 161291/2013
NYSCEF DOC. NO. 5 RECEIVED NYSCEF: 01/21/2014

EXHIBIT A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL - 2 2002

Richard W. Treharne, Ph.D.
Senior Vice President, Regulatory Affairs
Medtronic Sofamor Danek
1800 Pyramid Place
Memphis, Tennessee 38132

Re: P000058
InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device
Filed: January 12, 2001
Amended: January 12, March 19, May 9, July 31, August 24, September 25, October 9, November 21, and December 6, 7 and 26, 2001, January 22, February 8, March 19, April 2, 3, 12 (2), 15, 16, 17, 22, 26 and 30, May 9, 10, 14 and 28 and June 12 and 28, 2002
Procode: NEK

Dear Dr. Treharne:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. This device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, function deficit and/or neurological deficit and radiographic studies. These DDD patients may also have up to Grade I spondylolisthesis at the involved level. InFUSE™ Bone Graft/LT-CAGE™ devices are to be implanted via an anterior open or an anterior laparoscopic approach. Patients receiving the InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device should have had at least six months of nonoperative treatment prior to treatment with the InFUSE™ Bone Graft/LT-CAGE™ device. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the post-approval requirements outlined in the enclosure, you have agreed to provide the following data in a post-approval report:

1. In order to assess the long-term performance of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, please conduct a post-approval study to obtain a total of 6 years of postoperative data from a statistically-justified number of patients implanted with this device. The patients may be selected from either the IDE population, a population of post-approval implant patients or a combination of both.

   a. As part of the description of the post-approval study, you should provide a justification which includes:

      (1) the number of patients selected from each population (IDE vs. post-approval population);

      (2) the method(s) used to select the patients and sites; and

      (3) a description of the sample size calculations, including adjustments for lost-to-follow-up.

   b. The data from the post-approval study should be submitted to the FDA as part of your annual report and will include the following data collected biennially for each patient:

      (1) a description of any surgical interventions which include reoperations, removals, revisions, and supplemental fixations;

      (2) a radiographic assessment of fusion using the same criteria employed in the original IDE study;

      (3) an assessment of pain and function using the same criteria employed in the original IDE study.

2. Because of the unknown long-term device performance, particularly the resulting bony fusion characteristics, the post-approval study should also contain retrieval analyses of any InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device that is implanted and subsequently removed. This section of the post-approval study is not limited to the patient population described in item 1 above. Histological information (*e.g.*, bony ingrowth quality, bone quantity, response to potential wear debris, etc.) and metallurgical information (*e.g.*, metal wear, deformation, cracking, corrosion, etc.) should be collected and reported in the annual reports. This section of the post-approval study should continue for the duration of the study described in item 1 above.

3. Perform post-approval studies which assess the effects of rhBMP-2 on tumor promotion. These studies will include *in vitro* studies with primary tumor cell isolates.

4. Perform post-approval studies to investigate the potential for an immune response to rhBMP-2 to interfere in embryonic development in rabbits. Observations from this investigation may indicate a necessity to create a pregnancy monitoring database and/or modify your labeling.

5. Develop and validate a new antibody ELISA for antibodies to rhBMP-2 that has the potential to detect all antibody isotypes.

6. Develop and validate a neutralization assay for antibodies to rhBMP-2.

Complete final reports addressing the requests identified in items 3-6 above should be submitted as the reports become available. If these reports have not been submitted by the time of submission of the first PMA annual report, you should include an approximate timeline for submission in the annual reports, as well as updates on the studies' progress.

7. Provide the results of three additional assays, *i.e.*, silver stained SDS-PAGE, Edmans test and glycoform analysis, on the release specifications for the drug substance. These should be submitted as PMA reports.

Expiration dating for this device has been established and approved at three years for the Small and Medium InFUSE™ Bone Graft components, two years for the Large and Large II InFUSE™ Bone Graft components and five years for the LT-CAGE™ Lumbar Tapered Fusion Device component.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Mr. Aric D. Kaiser at (301) 594-2036.

Sincerely yours,

Daniel Schultz, M.D.
Deputy Director for Clinical
and Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Last Modified: 1-31-02

CONDITIONS OF APPROVAL

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e) or (f). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations that require a PMA supplement cannot be briefly summarized; therefore, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report (see below). FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Alternate submissions permitted under 21 CFR 814.39(f) for manufacturing process changes include the use of a 30-day Notice. The manufacturer may distribute the device 30 days after the date on which the FDA receives the 30-day Notice, unless the FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

1. Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

2. Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

   a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

   b. reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

1. A mix-up of the device or its labeling with another article.

2. Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:

   a. has not been addressed by the device's labeling; or

   b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency.

3. Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION.
The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers International and Consumer Assistance (DSMICA) at 301-443-8818.

FILED: NEW YORK COUNTY CLERK 01/21/2014 INDEX NO. 161291/2013
NYSCEF DOC. NO. 6 RECEIVED NYSCEF: 01/21/2014

EXHIBIT B

InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device
Important Medical Information

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training.

DESCRIPTION:
The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device consists of two components containing three parts– a tapered metallic spinal fusion cage, a recombinant human bone morphogenetic protein and a carrier/scaffold for the bone morphogenetic protein and resulting bone. The InFUSE™ Bone Graft component is inserted into the LT-CAGE™ Lumbar Tapered Fusion Device component to form the complete InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. **These components must be used as a system. The InFUSE™ Bone Graft component must not be used without the LT-CAGE™ Lumbar Tapered Fusion Device component.**

LT-CAGE™ Lumbar Tapered Fusion Device component
The LT-CAGE™ device consists of a hollow, perforated, machined cylinder with opposing flat sides. The cage has a tapered design with an angle of 8.8° and is available in diameters ranging from 14mm to 18mm at the narrow end of the taper, 17mm to 22 mm at the wide end of the taper and in lengths ranging from 20mm to 26mm. There are two holes on each of the two flat sides. On each of the two rounded aspects, there is a single rounded slot. The implants have a helical screw thread on the outer surface. One end of the device is closed. The other end is open to be filled with the InFUSE™ Bone Graft component.

The LT-CAGE™ implants are made from implant grade titanium alloy (Ti-6Al-4V) described by such standards as ASTM F136 or its ISO equivalent.

The LT-CAGE™ Lumbar Tapered Fusion Device component is sold separately from the InFUSE™ Bone Graft component, however, these two components must be used together. The package labeling for the LT-CAGE™ Lumbar Tapered Fusion Device contains complete product information for this component.

InFUSE™ Bone Graft component
InFUSE™ Bone Graft consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as dibotermin alfa) placed on an absorbable collagen sponge (ACS). The InFUSE™ Bone Graft component induces new bone tissue at the site of implantation. Based on data from non-clinical studies, the bone

formation process develops from the outside of the implant towards the center until the entire InFUSE™ Bone Graft component is replaced by trabecular bone.

rhBMP-2 is the active agent in the InFUSE™ Bone Graft component. rhBMP-2 is a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster ovary cell line.

rhBMP-2 and excipients are lyophilized. Upon reconstitution, each milliliter of rhBMP-2 solution contains: 1.5 mg of rhBMP-2; 5.0 mg sucrose, NF; 25 mg glycine, USP; 3.7 mg L-glutamic acid, FCC; 0.1 mg sodium chloride, USP; 0.1 mg polysorbate 80, NF; and 1.0 mL of sterile water. The reconstituted rhBMP-2 solution has a pH of 4.5, and is clear, colorless and essentially free from plainly visible particulate matter.

The ACS is a soft, white, pliable, absorbent implantable matrix for rhBMP-2. ACS is made from bovine Type I collagen obtained from the deep flexor (Achilles) tendon. The ACS acts as a carrier for the rhBMP-2 and acts as a scaffold for new bone formation.

Three sizes of the InFUSE™ Bone Graft component are available based on the internal volume of the LT-CAGE™ Lumbar Tapered Fusion Device component that is selected. The table below lists the appropriate InFUSE™ Bone Graft kit for the corresponding LT-CAGE™ Lumbar Tapered Fusion Device component size:

InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device Combinations				
LT-CAGE™ Lumbar Tapered Fusion Device		**Appropriate InFUSE™ Bone Graft Kit**		
Part #	Size (lead diameter, mm x length, mm)	Part #	Kit name (size in cc)	Reconstituted rhBMP-2/ACS graft volume
8941420	14x20	7510200	Small (2.8)	2.8ml
8941423	14x23	7510200	Small (2.8)	2.8ml
8941620	16x20	7510200	Small (2.8)	2.8ml
8941623	16x23	7510400	Medium (5.6)	5.6ml
8941626	16x26	7510400	Medium (5.6)	5.6ml
8941823	18x23	7510400	Medium (5.6)	5.6ml
8941826	18x26	7510600	Large Pre-Cut (8.0)	8.0ml
8941826	18x26	7510800	Large II (8.0)	8.0ml

Each kit contains all the components necessary to prepare the InFUSE™ Bone Graft component: the rhBMP-2 which must be reconstituted, sterile water, absorbable collagen sponges, syringes with needles, this package insert and

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instructions for preparation. The number of each item may vary depending on the size of the kit.

The rhBMP-2 is provided as a lyophilized powder in vials delivering either 4.2 mg or 12 mg of protein. After appropriate reconstitution, both configurations result in the same formulation and concentration (1.5 mg/mL) of rhBMP-2. The solution is then applied to the provided absorbable collagen sponge(s). The InFUSE™ Bone Graft component is prepared at the time of surgery and allowed a prescribed amount of time (no less than 15 minutes) before placement inside of the LT-CAGE™ Lumbar Tapered Fusion Device components. The Instructions for Preparation contain complete details on preparation of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device.

No warranties, express or implied, are made. Implied warranties of merchantability and fitness for a particular purpose or use are specifically excluded.

INDICATIONS:

The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L_4-S_1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients may also have up to Grade I spondylolisthesis at the involved level. Patients receiving the InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device should have had at least six months of nonoperative treatment prior to treatment with the InFUSE™ Bone Graft/LT-CAGE™ device. The InFUSE™ Bone Graft/ LT-CAGE™ Lumbar Tapered Fusion Device is to be implanted via an anterior open or an anterior laparoscopic approach.

CONTRAINDICATIONS

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be used in the vicinity of a resected or extant tumor.

- InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be used in pregnant women. The potential effects of rhBMP-2 on the human fetus have not been evaluated.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should not be implanted in patients with an active infection at the operative site or with an allergy to titanium or titanium alloy.

WARNINGS:

- Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on fetal development have not been assessed. In the clinical trial supporting the safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, 2/277 (0.7%) patients treated with InFUSE™ Bone Graft component and 1/127 (0.8%) patients treated with autograft bone developed antibodies to rhBMP-2. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive, thereby eliciting a more powerful immune response to BMP-2 with adverse consequences for the fetus. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that lack of BMP-2 activity, as might be induced by antibody formation, may cause neonatal death or birth defects.

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk.

- Women of childbearing potential should be advised not to become pregnant for one year following treatment with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device.

- The safety and effectiveness of the InFUSE Bone Graft component with other spinal implants, implanted at locations other than the lower lumbar spine, or used in surgical techniques other than anterior open or anterior laparoscopic approaches have not been established. When degenerative disc disease was treated by a posterior lumber interbody fusion procedure with cylindrical threaded cages, posterior bone formation was observed in some instances.

- The implantation of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device using an anterior laparoscopic surgical approach is associated with a higher incidence of retrograde ejaculation when compared to implantation using the an anterior open surgical approach.

PRECAUTIONS:

General

- The safety and effectiveness of repeat applications of the InFUSE™ Bone Graft component has not been established.

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- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device should only be used by surgeons who are experienced in spinal fusion procedures and have undergone adequate training with this device, for anterior laparoscopic and/or anterior open procedures.

- Two LT-CAGE™ Lumbar Tapered Fusion Device components should be implanted side by side at the surgical level whenever possible.

- The LT-CAGE™ Lumbar Tapered Fusion Device components and instruments must be sterilized prior to use according to the sterilization instructions provided in the package insert for that component, unless supplied sterile and clearly labeled as such.

- The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is intended for single use only. Discard unused product and use a new device for subsequent applications.

- Prior to use, inspect the packaging, vials and stoppers for visible damage. If damage is visible, do not use the product. Retain the packaging and vials and contact a Medtronic Sofamor Danek representative.

- Do not use after the printed expiration date on the label.

Hepatic and Renal Impairment

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device in patients with hepatic or renal impairment has not been established. Pharmacokinetic studies of rhBMP-2 indicate that the renal and hepatic systems are involved with its clearance.

Geriatrics

- Clinical studies of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device did not include sufficient numbers of patients 65 years and older to determine whether they respond differently from younger subjects.

Bone formation

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device has not been demonstrated in patients with metabolic bone diseases.

- While not specifically observed in the clinical study, the potential for ectopic, heterotopic or undesirable exuberant bone formation exists.

Antibody Formation/Allergic Reactions

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device has not been demonstrated in patients with autoimmune disease.

- The safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device has not been demonstrated in patients with immunosuppressive disease or suppressed immune systems resulting from radiation therapy, chemotherapy, steroid therapy or other treatments.

Immunogenicity

- As with all therapeutic proteins, there is a potential for immune responses to be generated to the InFUSE™ Bone Graft component. The immune response to the InFUSE™ Bone Graft components was evaluated in 349 investigational patients and 183 control patients receiving lumbar interbody fusions.

    - *Anti-rhBMP-2 antibodies:* 2/349 (0.6%) patients receiving the InFUSE™ Bone Graft component developed antibodies vs. 1/183 (0.5%) in the control group.

    - *Anti-bovine Type I collagen antibodies:* 18.1% of patients receiving the InFUSE™ Bone Graft component developed antibodies to bovine Type I collagen vs. 14.2% of control patients. No patients in either group developed anti-human Type I collagen antibodies.

    - The presence of antibodies to rhBMP-2 was not associated with immune mediated adverse events such as allergic reactions. The neutralizing capacity of antibodies to rhBMP-2 is not known.

- The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally, the incidence of antibody detection may be influenced by several factors including sample handling, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to the InFUSE™ Bone Graft component with the incidence of antibodies to other products may be misleading.

ADVERSE EVENTS:

The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device was implanted in 288 investigational patients and compared to 139 control patients who received an LT-CAGE™ Lumbar Tapered Fusion Device filled with iliac crest autograft. The investigational patients were implanted with the device via either an open anterior surgical approach or a laparoscopic anterior surgical approach. The control patients were implanted only via the open anterior surgical approach.

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Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

ADVERSE EVENTS

(INFUSE™ Bone Graft/LT-Cage™ Device data combined from all experience with the device)

	Surgery		Postoperative (1 day - <4 Weeks)		6 Weeks (≥4 Wks - <9 Weeks)		3 Months (≥9 Wks - <5 Months)		6 Months (≥5 Mos - <9 Months)		12 Months (≥9 Mos - <19 Months)		24 Months (≥19 Mos - <30 Months)		# of Patients Reporting & Total adverse events	
Complication	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Inves.	Control	Investigational # (% of 288) total events	Control #(% of 139) total events
Anatomical/Technical Difficulty	10	3	0	0	0	0	0	0	0	0	0	0	0	0	10 (3.5) 10	3 (2.2) 3
Back and/or Leg Pain	0	0	1	4	11	5	10	5	14	4	20	7	6	8	65 (22.6) 72	30 (21.6) 33
Cancer	0	0	0	0	0	0	0	1	0	0	1	0	0	0	1 (0.3) 1	1 (0.7) 1
Cardio/Vascular	2	0	4	5	6	2	1	3	2	1	3	2	0	1	15 (5.2) 18	12 (8.6) 14
Death	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0 (0.0) 0	1 (0.7) 1
Dural Injury	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0 (0.0) 0	1 (0.7) 1
Gastrointestinal	1	0	38	22	2	0	5	1	7	1	9	3	4	5	53 (18.4) 67	27 (19.4) 32
Graft Site Related	0	0	0	0	0	8	0	0	0	0	0	0	0	0	0 (0.0) 0	8 (5.8) 8
Implant Displacement/ Loosening	0	0	1	1	3	0	1	0	0	0	0	0	0	0	5 (1.7) 5	1 (0.7) 1
Infection	0	0	19	9	8	4	4	1	5	1	3	0	0	2	35 (12.2) 39	16 (11.5) 17
Malpositioned Implant	5	0	0	0	0	0	0	0	0	0	0	0	0	0	5 (1.7) 5	0 (0.0) 0
Neurological	0	0	7	5	7	3	5	2	5	2	10	3	5	7	36 (12.5) 39	21 (15.1) 22
Non-Union *	0	0	0	0	0	0	1	0	1	3	2	0	1	1	5 (1.7) 5	4 (2.9) 4
Non-Union **	0	0	0	1	0	1	3	0	3	4	4	6	1	1	11 (3.8) 11	13 (9.4) 13
Other	6	6	17	11	7	2	3	4	8	4	14	8	9	8	59 (17.4) 64	37 (26.6) 43
Other Pain	0	0	1	1	2	0	4	2	5	1	7	6	6	3	21 (7.3) 25	12 (8.6) 13
Respiratory	0	0	3	2	1	0	0	0	1	0	0	1	0	1	5 (1.7) 5	4 (2.9) 4
Retrograde Ejaculation	0	0	4	1	5	0	1	0	0	0	2	0	0	0	11 (7.9)[1] 12	1 (1.4)[2] 1
Spinal Event	0	0	1	2	0	0	6	2	8	3	8	8	4	2	24 (8.3) 27	16 (11.5) 17
Subsidence	0	0	3	2	2	0	1	0	1	0	0	0	0	0	7 (2.4) 7	2 (1.4) 2
Trauma	0	0	4	4	5	3	11	6	14	5	27	9	11	7	60 (20.8) 72	29 (20.9) 34
Urogenital	1	0	20	5	2	0	2	2	6	1	2	1	4	2	33 (11.5) 37	10 (7.2) 11
Vascular Intra-Op	15	5	0	0	0	0	0	0	0	0	0	0	0	0	14 (4.9) 15	5 (3.6) 5
Vertebral Fracture	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1 (0.3) 1	0 (0.0) 0
Any Adverse Event															214 (74.3)	114 (82.0)

* Non-union adverse events that have not resulted in a second surgery.
** Non-union adverse events that have resulted in a second surgery.
[1] Percent of 140 males.
[2] Percent of 70 males.

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The reported rates of several adverse events were high, but similar, in both the investigational and control groups. These events included back and leg pain, neurological events, gastrointestinal events, spinal events, cardiovascular events and infection.

Some of the reported adverse events required surgical interventions subsequent to the initial surgery. The number of subjects requiring a second surgical intervention was 10.4% (30/288) in the investigational groups and 13.7% (19/139) in the control group. The majority of supplemental fixations were due to painful nonunion.

Urogenital events occurred with greater frequency in the investigational groups (11.5%) compared to the control group (7%). Retrograde ejaculation rates were greater in the investigational groups (11 subjects) compared to the control group (1 subject) with the majority of events occurring in the early postoperative period.

The incidence of adverse events that were considered device related, including implant displacement/loosening, implant malposition and subsidence were all greater in the investigational groups compared to the control group. The rates of these events were low, however, and may be partially attributed to a learning curve associated with the laparoscopic surgical approach. The rate of nonunion requiring secondary surgery in the investigational groups was comparable to that of the control group. One death was reported - a control group subject with cardiovascular disease.

Potential Adverse Events:

The following is a list of potential adverse events which may occur with spinal fusion surgery with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. Some of these adverse events may have been previously reported in the adverse events table.

- Bone fracture.
- Bowel or bladder problems.
- Cessation of any potential growth of the operated portion of the spine. Loss of spinal mobility or function.
- Change in mental status.
- Damage to blood vessels and cardiovascular system compromise.
- Damage to internal organs and connective tissue.
- Death.

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- Development of respiratory problems.
- Disassembly, bending, breakage, loosening, and/or migration of components.
- Dural tears.
- Ectopic and/or exuberant bone formation.
- Fetal development complications.
- Foreign body (allergic) reaction.
- Gastrointestinal complications.
- Incisional complications.
- Infection.
- Insufflation complications.
- Neurological system compromise.
- Nonunion (or pseudarthrosis), delayed union, mal-union.
- Postoperative change in spinal curvature, loss of correction, height, and/or reduction.
- Retrograde ejaculation.
- Scar formation.
- Tissue or nerve damage.

Note: Additional surgery may be necessary to correct some of these potential adverse events.

CLINICAL RESULTS:

Clinical data to support the safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device were collected as part of a prospective, multi-center pivotal study that consisted of randomized and non-randomized arms. The randomized arm contained two groups, one investigational and one control. The control group was implanted with the LT-CAGE™ Lumbar Tapered Fusion Device filled with iliac crest autograft bone, while the investigational group was implanted with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. In both

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cases, the surgical approach was an open anterior approach. The non-randomized arm contained only an investigational group, where subjects were implanted with the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device through a laparoscopic anterior approach. The control group from the randomized arm was used as the control for the non-randomized arm.

Neither the investigators nor the subjects were blinded to the treatment. Subject blinding was not possible due to the second surgical site resulting from the need to collect the iliac crest grafts. The potential for investigator bias in the clinical outcome parameters was reduced by having the subjects rate their outcome using objective self-assessments. The radiographic outcome parameters were performed by independent radiologists who were blinded to treatment. These were the only radiographic evaluations used for determining radiographic success.

The indication studied was degenerative disc disease (DDD) accompanied by back pain with or without leg pain at a single level between L_4 and S_1 confirmed by history and radiographic studies.

Clinical and radiographic effectiveness parameters

Patients were evaluated preoperatively (within 6 months of surgery), intraoperatively, and postoperatively at 6 weeks, 3, 6, 12 and 24 months and biennially thereafter until the last subject enrolled in the study had been seen for their 24 month evaluation. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial. At each evaluation timepoint, the primary and secondary clinical and radiographic outcome parameters were evaluated. Success was determined from data collected during the initial 24 months of follow-up. Antibodies to rhBMP-2 and bovine Type I collagen were assessed preoperatively and at 3 months post-operatively. Antibodies to human Type I collagen were assessed if the antibody response to bovine Type I collagen was positive.

Primary and secondary clinical and radiographic effectiveness outcome parameters were evaluated for all treated subjects at all follow-up evaluation timepoints identified above. The primary clinical parameters assessed were of pain, function and neurological status. The secondary clinical outcome parameters assessed were general health status, back and leg pain, donor site pain (control subjects only), patient satisfaction and patient global perceived effect of the treatment. The primary radiographic outcome parameter consisted of evaluations of fusion, while the secondary radiographic assessment was disc height.

Fusion was evaluated at 6, 12 and 24 months post-op using plain radiographs (AP, lateral and flexion/extension films) and high resolution thin-slice CT scans (1mm slices with 1mm index on axial sagittal and coronal reconstructions). Fusion was defined as the presence of bridging bone connecting the inferior and superior

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vertebral bodies; a lack of motion on flexion/extension (≤ 3mm of translation and < 5° of angulation); and no evidence of radiolucencies over more that 50% of either implant. Fusion success was defined as the presence of all of these parameters plus the lack of a second surgical intervention resulting from a non-union. All assessments were made from the plain films except for the assessment of bridging bone, which was made using the CT scans only if bridging bone could not be visualized on the plain film.

Pain and function were measured using the Oswestry Low Back Pain Disability Questionnaire. Success was defined as a 15 point improvement in the Oswestry score from the pre-op baseline score.

Neurological status consisted of measurements of four parameters - motor, sensory, reflexes, and straight leg raise (SLR). Neurological status success was defined as maintenance or improvement of the pre-op baseline score for each parameter. Overall neurological status success required that each individual parameter be a success for that subject to be counted as a success.

Patient demographics and accountability

A total of 143 open approach investigational and 136 control patients were enrolled in the randomized arm of the study and received the device. A total of 134 subjects were enrolled in the non-randomized arm of the study and received the device. For the majority of the demographic parameters, there were no differences in pre-op demographics across the three populations.

Surgical results and hospitalization

Surgical and hospitalization information			
	Investigational Open Surgical Approach	Control Open Surgical Approach	Investigational Laparoscopic Surgical Approach
mean operative time (hrs)	1.6	2.0	1.9
mean EBL (ml)	109.8	153.1	146.1
hospitalization (days)	3.1	3.3	1.2

statistically different from control

Clinical and radiographic effectiveness evaluation

Individual subject success was defined as success in each of the primary clinical and radiographic outcome parameters. Success for these parameters included:

1. the presence of radiographic fusion;
2. an improvement of at least 15 points from the baseline Oswestry score;
3. maintenance or improvement in neurological status;
4. the presence of no serious adverse event classified as implant-associated or implant/surgical procedure-associated; and
5. no additional surgical procedure classified as "Failure."

Study success was expressed as the number of individual subjects categorized as a success divided by the total number of subjects evaluated. The table below describes the success rates for the individual primary outcome parameters and overall success. All success rates were based on the data from the 24 month follow-up evaluation and posterior probabilities of success were calculated using Bayesian statistical methods.

Posterior Probabilities of Success at 24 Months			
Primary outcome variable	Investigational Open Surgical Approach	Control Open Surgical Approach	Investigational Laparoscopic Surgical Approach
	Posterior Mean (95% HPD Credible Interval)	Posterior Mean (95% HPD Credible Interval)	Posterior Mean (95% HPD Credible Interval)
Fusion	92.8% (88.5%, 96.9%)	88.1% (82.6%, 99.3%)	93.0% (87.9%, 97.5%)
Oswestry	71.0% (63.4%, 78.7%)	70.9% (63.1%, 79.1%)	83.0% (75.6%, 90.5%)
Neurologic	81.0% (74.5%, 87.9%)	81.7% (74.9%, 88.7%)	89.0% (83.1%,94.8%)
Overall success	57.1% (49.2%, 65.7%)	56.7% (48.3%, 65.0%)	68.0% (59.3%, 76.5%)

The probability (also called the posterior probability) that the 24 month overall success rate for the investigational groups was equivalent to the 24 month success rate for the control group was 99.4% for the open surgical approach investigational group and almost 100% for the laparoscopic surgical approach investigational group.

For a future patient receiving the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device via the open anterior surgical approach, the chance (the predictive probability) of overall success at 24 months would be 57.1% for the open surgical approach. Given the results of the trial, there is a 95% probability that the chance of success ranges from 49.2% to 65.7%. For a future patient receiving the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device via the anterior laparoscopic surgical approach, the chance of overall success at 24 months would be 68.0%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 59.3% to 76.5%. For a future patient receiving the control treatment, the chance of overall success at 24 months would be 56.7%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 48.3% to 65.0%.

Safety and immune response evaluation

The assessment of safety consisted of an evaluation of the reported adverse events, as well as an evaluation of antibodies to rhBMP-2, bovine Type I collagen and human Type I collagen. The complete list of complications, adverse events and subsequent interventions is described in the Adverse Events section above. The presence of antibodies were assessed at the pre-op and 3 month post-op visits using ELISA. If there was a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen. The screening ELISA cutpoint for positive

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antibody responses was set to 5 times the standard deviation of sera from normal human donors. Subjects were considered to have an elevated immune response if the preoperative test was negative (titer < 50) and postoperative test was positive (titer ≥ 50) or if the preoperative test was positive and the postoperative test was positive with a three-fold higher titer than the preoperative test.

There were 3 subjects who had positive antibody responses to rhBMP-2 – 1 subject in each of the study groups. The rates of positive antibody response to rhBMP-2 were 0.7% in the open surgical approach investigational group and 0.8% in the laparoscopic surgical approach investigational and open surgical approach control groups. While there is a theoretical possibility that antibodies to rhBMP-2 could neutralize endogenous BMP-2, thereby interfering with subsequent bone healing, this was not observed during the course of the study.

Sixty-six subjects were considered to have an authentic elevated antibody response to bovine Type I collagen - 18 open surgical approach investigational subjects, 32 laparoscopic surgical approach investigational subjects and 16 control subjects. No subjects had positive responses to human Type I collagen.

An evaluation was performed on the impact of a positive antibody response on overall success and fusion success. There was very little difference in overall and individual success when antibody status was taken into consideration.

During the course of the study, 6 pregnancies were reported – one in the control group and five in the investigational groups. Two of the four pregnancies that occurred in the laparoscopic approach group resulted in first trimester miscarriages. The other three pregnancies in the investigational groups resulted in live births with no reported complications. None of the pregnant subjects had antibody responses to rhBMP-2 or Type I collagen (bovine or human), that were detectable to the limits of the sensitivity of the assay.

Two cases of cancer were diagnosed during the course of the pivotal study – one in an investigational group and one in the control group. An investigational subject was found to have pancreatic cancer while a control subject was found to have breast cancer. No additional information is available on these subjects, *e.g.*, BMP-2 receptor expression.

HOW SUPPLIED

InFUSE™ Bone Graft component is supplied in three kit sizes containing all the components necessary to prepare this portion of the device, *i.e.*, the collagen sponge(s), a vial with the lyophilized growth factor, a vial with sterile water for reconstituting the growth factor, syringes and needles. The LT-CAGE™ Lumbar

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Tapered Fusion Device component is supplied in seven sizes which must be properly selected based on a specific patient's anatomy.

STORAGE CONDITIONS

Store the InFUSE™ Bone Graft component at room temperature (15 – 25 degrees Centigrade (59 to 77° F)). The LT-CAGE™ Lumbar Tapered Fusion Device component should also be stored at room temperature.

DOSAGE AND ADMINISTRATION

InFUSE™ Bone Graft component is prepared immediately prior to use from a kit containing all necessary components. Once prepared, the InFUSE™ Bone Graft component contains rhBMP-2 at a concentration of 1.5 mg/mL.

The size of the InFUSE™ Bone Graft component kit and the volume of InFUSE™ Bone Graft component to be implanted are determined by the internal volume of the LT-CAGE™ Lumbar Tapered Fusion Device components which are utilized. The patient's anatomy will determine the size of the LT-CAGE™ components to be used. The InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device surgical technique provides more information on templating to determine the appropriate size LT-CAGE™ Lumbar Tapered Fusion Device component.

DIRECTIONS FOR USE

InFUSE™ Bone Graft component is prepared at the time of surgery in the surgical suite by reconstituting the lyophilized rhBMP-2 with sterile water (See Instructions for Preparation), and then uniformly applying the reconstituted rhBMP-2 solution to the ACS. The InFUSE™ Bone Graft component is then inserted into the LT-CAGE™ Lumbar Tapered Fusion Device component. The complete device is then implanted through an anterior open or laparoscopic surgical approach (See the Surgical Technique manual). If the InFUSE™ Bone Graft component is not used within two hours after reconstitution, it must be discarded.

The InFUSE™ Bone Graft component must not be sterilized by the hospital. The LT-CAGE™ Lumbar Tapered Fusion Device component, if not supplied sterile, should be sterilized before insertion of the InFUSE™ Bone Graft component. Refer to the package insert for the LT-CAGE™ Lumbar Tapered Fusion Device component for information on packaging, cleaning/decontamination and sterilization of this component and its instruments.

PRODUCT COMPLAINTS:

Any health care professional (e.g., customer or user of this system of products), who has any complaints or who has experienced any dissatisfaction in the quality, identification, durability, reliability, safety, effectiveness and/or performance of this product, should notify the distributor, Medtronic Sofamor Danek. Further, if any of the

implanted InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device components ever "malfunction," (i.e., do not meet any of their performance specifications or otherwise do not perform as intended), or are suspected of doing so, the distributor should be notified immediately (1-800-933-2635). If any Medtronic Sofamor Danek product ever "malfunctions" and may have caused or contributed to the death or serious injury of a patient, the distributor should be notified immediately by telephone, fax or written correspondence. When filing a complaint, please provide the component name and number, lot number, your name and address, the nature of the complaint and notification of whether a written report from the distributor is requested.

DEVICE RETRIEVAL EFFORTS:

Should it be necessary to remove an InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device, please call Medtronic Sofamor Danek prior to the scheduled surgery to receive instructions regarding data collection, including histopathological, mechanical and adverse event information.

IN USA

Customer Service Division **Telephone:** 800-933-2635
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STAFF REPORT ON MEDTRONIC'S INFLUENCE ON INFUSE CLINICAL STUDIES

PREPARED BY THE STAFF OF THE

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UNITED STATES SENATE

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Introduction

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs. As the Chairman and a senior member and former Chairman of the Committee, we have a responsibility to the more than 100 million Americans who receive health care coverage under these programs to oversee their proper administration and ensure the taxpayer dollars are appropriately spent on safe and effective medical treatments. On June 21, 2011, the Committee staff initiated an inquiry into whether Medtronic, Inc. (Medtronic or the Company) improperly influenced peer-reviewed studies of Medtronic's bone-growth product InFuse, also known as bone morphogenetic protein 2 (BMP–2).

The Committee staff's inquiry was prompted by reports alleging that physician authors who had financial ties to Medtronic failed to report dangerous side effects associated with InFuse. These dangerous side effects were subsequently reported by medical researchers that did not have financial relationships with the company.[1]

A week later, on June 28, 2011, *The Spine Journal* devoted an entire publication to exposing a pattern of academic surgeons with financial ties to Medtronic omitting mention of serious side effects associated with InFuse.[2] The analysis, led by Dr. Eugene Carragee at Stanford University, identified 13 studies sponsored by Medtronic where there was absolutely no reporting of adverse events associated with InFuse.[3] However, *The Spine Journal* found the rate of adverse events related to the use of InFuse ranged from 10%–50%.[4]

In response to the June 21, 2011 request by Chairman Baucus and Senator Grassley, Medtronic produced more than 5,000 documents pertaining to the 13 rhBMP–2 studies analyzed in *The Spine Journal*. The documents included the amount of money Medtronic paid to physician authors, e-mail communication between Medtronic employees, and e-mails between Medtronic employees and physician authors pertaining to drafts of peer-reviewed articles reporting the results of the Medtronic-sponsored clinical trials. After thorough review of the documents submitted by Medtronic and other materials, the Committee staff makes the following findings:

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[1] "New Study Links Spine Product From Medtronic to Risk of Sterility in Men," *New York Times*, May 25, 2011; "Researchers get royalties, papers omit sterility link," *Milwaukee Journal Sentinel*, May 25, 2011.

[2] "Spine Experts Repudiate Medtronic Studies," *New York Times*, June 28, 2011.

[3] "A critical review of recombinant human bone morphogenetic protein–2 trials in spinal surgery: emerging safety concerns and lessons learned," *The Spine Journal* 11 (2011) 471–491 at *http://www.spine.org/Documents/TSJJune2011_Carragee_etal_CriticalRev.pdf*.

[4] *Id.*

Findings

- Medtronic was heavily involved in drafting, editing, and shaping the content of medical journal articles authored by its physician consultants who received significant amounts of money through royalties and consulting fees from Medtronic. The company's significant role in authoring or substantively editing these articles was not disclosed in the published articles. Medical journals should ensure industry role contributions be fully disclosed.
- Medtronic paid a total of approximately $210 million to physician authors of Medtronic-sponsored studies from November 1996 through December 2010 for consulting, royalty, and other miscellaneous arrangements.
- An e-mail exchange shows that a Medtronic employee recommended against publishing a complete list of adverse events possibly associated with InFuse in a 2005 *Journal of Bone and Joint Surgery* article.
- Medtronic officials inserted language into studies that promoted InFuse as a better technique than taking a bone graft from the pelvic bone (autograft technique) by emphasizing the pain of the autograft technique.
- Documents indicate that Medtronic prepared Dr. Hal Mathew's remarks to the U.S. Food and Drug Administration (FDA) advisory panel meeting prior to InFuse being approved. At the time, Dr. Mathews was a private physician but was hired as a vice president at Medtronic in 2007.
- Medtronic documents show the company unsuccessfully attempted to adopt weaker safety rules for a clinical trial studying InFuse in the cervical spine that would have allowed the company to continue the trial in the event that patients experienced severe swelling in the neck.

Background on InFuse

In 2002, the FDA approved InFuse (also known as rh–BMP–2 or bone morphogenetic protein 2), a genetically engineered protein that stimulates bone growth for use in spinal fusion surgery in conjunction with the LT-Cage Lumbar Tapered Fusion Device to treat degenerative disc disease in the lower spine.[5]

Degenerative disc disease is a condition where the discs between spinal vertebrae deteriorate with age and can be a source of back pain. In some cases, degenerative disc disease is treated with spinal fusion surgery where the degenerated disc is removed and the adjacent vertebrae are joined together with a bone graft material to eliminate pain.[6] Medtronic promotes the use of InFuse for spinal surgery as a way to eliminate surgery and pain associated with the

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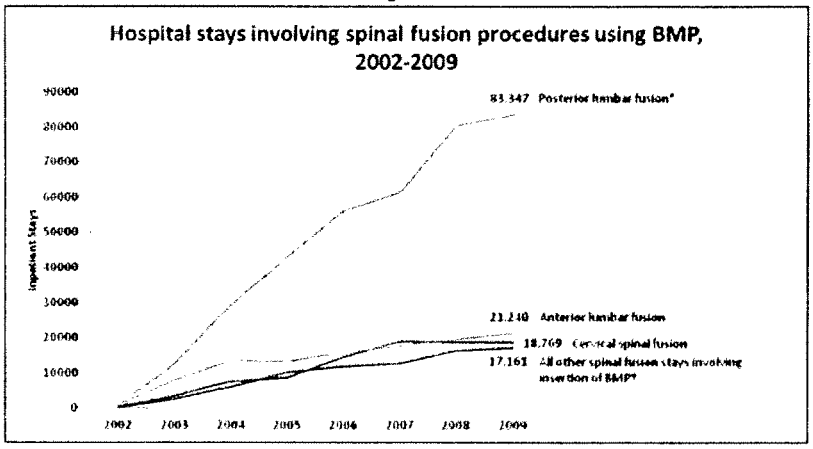
[5] See FDA's brief overview of the InFUSE™ Bone Graft/LT–CAGE™ Lumbar Tapered Fusion Device at *http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm083423.htm.*

[6] Handout on Health: Back Pain, April 2012, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH at *http://www.niams.nih.gov/health_info/back_pain/default.asp.*

autograft procedure, where bone is harvested from the patient's hip for use in the spine.[7]

The FDA's 2002 approval of InFuse was limited to spinal surgeries using the anterior lumbar interbody fusion (ALIF) technique. The ALIF approach allows surgeons to access the spine through the abdomen but does not involve "retraction of the spinal nerves and neurologic structures" which decreases the "risk of neurologic injury."[8] During the FDA advisory committee hearing prior to the approval of InFuse, concerns were expressed about the high potential for off-label use.[9] The Agency for Healthcare Research and Quality (AHRQ) estimates that, in 2009, only 21,240 of 140,467 spinal fusion surgeries with InFuse were performed using the anterior lumbar technique. The remaining 119,227 hospital stays were associated with off-label spinal fusion techniques such as posterior lumbar fusion and cervical spinal fusion.[10] This AHRQ estimate is consistent with a widely cited figure that "at least 85% of InFuse use is now off-label."[11]

Figure 1.



*Includes posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), and extreme lateral interbody fusion (XLIF).
†Includes anterior dorsal fusion, posterior dorsal fusion, lateral transverse lumbar fusion, and posterolateral lumbar fusion.
Source: Agency for Healthcare Reserach and Quality, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 2002–2009.

[7] Questions and Answers—Infuse Bone Graft and LT Cage Device," available on Medtronic website.
[8] "Anterior Lumbar Interbody Fusion (ALIF)—Overview and Indications," USC Center for Spinal Surgery, University of Southern California at *http://www.uscspine.com/treatment/anterior-lumbar-fusion.cfm.*
[9] FDA Advisory Panel Meeting, January 10, 2002, FDA at *http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3828t1.htm.*
[10] "Trends in Hospital Stays For Spinal Fusion Using Recombinant Human Bone Morphogenetic Protein," Healthcare Cost and Utilization Project, AHRQ.
[11] "Medtronic Surgeons Held Back, Study Says," *Wall Street Journal*, June 29, 2011.

Table 1.

Hospital stays involving spinal fusion procedures using BMP, 2002–2009

	2002	2003	2004	2005	2006	2007	2008	2009
Cervical spinal fusion	377	3,656	7,590	8,805	14,548	18,955	18,887	18,769
Anterior lumbar fusion	920	8,166	13,511	13,239	15,870	17,774	19,820	21,240
Posterior lumbar fusion *	978	12,667	29,460	42,997	56,185	61,382	80,367	83,347
All other spinal fusion stays involving insertion of BMP †	174	2,783	6,126	10,351	11,828	12,862	16,329	17,161

* Includes posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), and extreme lateral interbody fusion (XLIF).

† Includes anterior dorsal fusion, posterior dorsal fusion, lateral transverse lumbar fusion, and posterolateral lumbar fusion.

Source: Agency for Healthcare Reserach and Quality, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 2002–2009.

In 2008, the FDA published a public health notification linking the off-label use of InFuse in the cervical spine with life-threatening swelling in patient's throats and necks.[12] The *Wall Street Journal* reported at the time that "the agency . . . received 38 reports over four years of side effects, mainly swelling of neck and throat tissue, which resulted in compression of the airway and other structures in the neck."[13] In addition, the *Wall Street Journal* reported that "[a]t least three-quarters of the roughly 200 'adverse events' reported to the FDA involve off-label uses of InFuse."[14]

In March 2011, the FDA declined to approve a higher-strength version of InFuse called Amplify due to concerns that the product may cause cancer.[15] Later that year, Dr. Eugene Carragee of Stanford University presented data at a spinal surgeon conference that he believes demonstrates that the patient group that received Amplify experienced a "significantly higher number of cancers . . . compared to a control group that received a bone graft" but was not reported in a 2009 industry-sponsored publication on Amplify.[16] Dr. Carragee told the *New York Times* that "doctors often administered InFuse off-label at levels significantly above the recommended dosages, ones that approach or exceed the amount of rhBMP–2 found in a dose of Amplify."[17]

Medtronic's Financial Relationships to Physician Authors of rhBMP–2 Studies

Medtronic produced a list of payments to physician authors of the 13 industry studies that were the subject of *The Spine Journal* article published in June 2011. The physicians who received pay-

[12] "Medtronic Product Linked to Surgery Problems," *Wall Street Journal*, September 4, 2008.
[13] *Id.*
[14] *Id.*
[15] "FDA sets back Medtronic spine product," *Star Tribune*, March 10, 2011.
[16] "Data Links High Doses of Bone Drug to Cancer," November 3, 2011, *New York Times* at *http://www.nytimes.com/2011/11/04/health/research/amplify-by-medtronic-may-raise-chance-of-cancer-data-shows.html*.
[17] *Id.*

ments of over $1 million from Medtronic from 1996 through 2010 are listed below along with the amount of money received.

Year	Scott D. Boden	Charles L. Branch	J. Kenneth Burkus	Concept Properties, LLC [18]	Curtis A. Dickman
1996	$18,750.00	—	—	—	—
1997	$75,000.00	—	—	—	$5,003.70
1998	$75,000.00	$140,703.15	$18,700.00	—	$73,239.25
1999	$86,957.00	$49,238.87	$34,712.12	—	$130,352.64
2000	$75,000.00	$104,495.00	$29,285.75	—	$41,419.50
2001	$73,750.00	$150,000.00	$149,920.00	$636,182.00	$56,960.00
2002	$80,000.00	$201,997.75	$220,539.50	$1,028,882.00	$72,881.00
2003	$82,500.00	$180,219.99	$268,742.50	$1,226,179.00	$316,215.00
2004	$138,500.00	$175,473.78	$360,447.78	$4,992,137.00	$320,045.99
2005	$1,364,100.00	$127,087.44	$331,070.44	$13,141,165.00	$339,338.00
2006	$1,782,550.00	$136,390.58	$613,849.71	$8,842,157.00	$401,138.77
2007	$3,400,875.00	$114,159.39	$719,281.84	$9,683,098.00	$383,192.00
2008	$21,543,052.00	$487,688.50	$1,928,503.35	$9,159,891.00	$388,248.00
2009	—	$460,319.35	$732,563.85	$7,117,112.00	$355,809.00
2010	—	$827,851.81	$972,719.99	$9,004,465.00	$389,099.00
Total	$28,796,034.00	$3,155,625.61	$6,380,336.83	$64,831,268.00	$3,272,941.85

Year	John R. Dimar, III	Steven D. Glassman	Matthew F. Gornet	Regis W. Haid, Jr.	John G. Heller
1996	$6,250.00	$6,250.00	—	—	—
1997	$27,000.00	$25,000.00	$1,880.00	$27,500.00	—
1998	$50,000.00	$50,000.00	—	$216,842.44	$10,892.00
1999	$52,022.65	$52,216.41	$29,900.00	$1,019,832.54	$70,817.57
2000	$50,000.00	$50,976.43	$16,369.97	$1,507,242.15	$30,000.00
2001	$188,428.00	$194,528.00	$15,128.00	$1,394,390.61	$37,975.10
2002	$100,100.00	$71,750.00	$4,762.00	$1,669,745.11	$1,161.73
2003	$116,283.65	$138,941.44	$10,194.00	$1,957,742.86	$49,191.50
2004	$104,043.67	$146,137.07	$17,924.00	$2,484,450.94	$42,957.44
2005	$147,207.99	$248,019.59	$67,763.93	$2,473,518.00	$154,835.70
2006	$236,306.95	$155,753.16	$238,787.49	$2,454,569.00	$149,215.39
2007	$130,767.60	$257,926.16	$649,542.33	$2,626,576.07	$330,792.15
2008	$234,094.50	$187,605.50	$1,181,039.87	$2,467,911.23	$288,957.11
2009	$160,551.00	$88,139.80	$892,500.87	$2,525,743.88	$255,236.24
2010	$163,310.20	$75,019.80	$859,983.76	$2,723,749.13	$352,404.36
Total	$1,766,366.21	$1,748,263.36	$3,985,776.22	$25,549,813.96	$1,774,436.29

Year	Inspire, LLC [19]	Gerald E. Rodts, Jr.	Volker Sonntag	Ensor E. Transfeldt	Thomas A. Zdeblick
1996	—	—	—	$12,500.00	$95,185.34
1997	—	—	$34,745.92	$50,000.00	$422,668.65
1998	—	$25,065.54	$207,622.16	$56,196.00	$838,794.89
1999	—	$44,748.08	$795,053.91	$61,219.28	$1,131,463.17
2000	—	$ 152,496.47	$1,756,041.55	$56,170.90	$1,037,381.49
2001	—	$140,343.39	$1,036,993.00	$71,117.56	$1,984,356.45
2002	—	$172,278.04	$1,646,050.49	$115,315.16	$3,471,930.41
2003	—	$142,025.68	$1,904,689.00	$258,912.62	$4,580,361.62
2004	—	$161,149.02	$2,728,639.00	$299,477.72	$4,447,269.00
2005	—	$303,877.98	$2,202,595.00	$30,474.70	$3,950,516.08
2006	—	$396,139.57	$2,090,998.00	$206,388.76	$3,469,863.71
2007	$247,365.00	$629,451.53	$2,163,661.90	$722,779.00	$2,961,272.00
2008	$329,998.00	$581,984.26	$2,271,477.00	$548,584.74	$2,521,170.00
2009	$698,829.00	$432,403.00	$1,772,361.00	$483,254.00	$1,582,156.00
2010	$1,632,813.00	—	$2,241,156.00	$589,930.00	$1,674,351.00
Total	$2,909,005.00	$3,181,962.56	$22,852,083.93	$3,562,320.44	$34,168,739.81

More detailed information concerning Medtronic's physician payments is available in the appendix to this report.[20]

[18] According to filings with the Office of the Secretary of State of Kentucky, John R. Dimar, III and Steven D. Glassman are listed as current officers of Concept Properties, LLC as of June 18th, 2012.

[19] According to an attachment to Medtronic's June 21, 2011 letter to the Committee, the Company "believes that Inspire, LLC is owned by physicians including Dr. Transfeldt."

[20] See page 22.

Medtronic Employees Were Substantively Involved in Producing Journal Articles Authored by the Company's Physician Consultants

A review of the documents Medtronic provided to the Committee demonstrates that Medtronic employees, including employees working for its marketing department, collaborated with physician authors, many of whom had significant financial relationships with Medtronic, to draft the following studies:

- Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP–2 with tapered interbody cages. *J. Spinal Disord. Tech.* 2002; 15:337–49.[21]
- Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein–2. *Spine* 2002.[22]
- Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT–CAGE lumbar tapered fusion device. *J. Spinal Disord. Tech.* 2003.[23]
- Baskin DS, Ryan P, Sonntag V, et al. A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein–2 with the CORNERSTONE–SR allograft ring and the ATLANTIS anterior cervical plate. *Spine* 2003.[24]
- Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine* 2003.[25]
- Haid RW, Branch CL, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. *Spine J.* 2004.[26]
- Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP–2 in combination with structural cortical allografts

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[21] See correspondence and draft articles MSD–R062111–033531—MSD–R062111–033562; MSD–R062111–033566—MSD–R062111–033568—MSD–R062111–033612; MSD–R062111–033616; MSD–R062111–040460—MSD–R062111–040463; MSD–R062111–077880—MSD–R062111–077920; MSD–R062111–033822—MSD–R062111–033862; MSD–R062111–080852—MSD–R062111–080894.

[22] See correspondence and draft articles MSD–R062111–033047—MSD–R062111–033079; MSD–R062111–033225—MSD–R062111–033256; MSD–R062111–033631—MSD–R062111–033668; MSD–R062111–033748—MSD–R062111–033784; MSD–R062111–055062—MSD–R062111–055067; MSD–R062111–033972—034006.

[23] See correspondence and draft articles MSD–R062111–064299—MSD–R062111–064284; MSD–R062111–064346—MSD–R062111–064373; MSD–R062111–067943—MSD–R062111–067971; MSD–R062111–080895—MSD–R062111–080899; MSD–R062111–080956—MSD–R062111–080983.

[24] See correspondence and draft articles MSD–R062111–034007—MSD–R062111–034039; MSD–R062111–034087—MSD–R062111–034189.

[25] See correspondence and draft articles MSD–R062111–033112—MSD–R062111–033126; MSD–R062111–064232—MSD–R062111—064245; MSD–R062111–033434—MSD–R062111–033450; MSD–R062111–033669—MSD–R062111–033688.

[26] See correspondence and draft articles MSD–R062111–040537—MSD–R062111–040561; MSD–R062111–069990—MSD–R062111–069997; MSD–R062111–078885—MSD–R062111–078895; MSD–R062111–034221—MSD–R062111–034224; MSD–R062111–068009—MSD–R062111–068070; MSD–062111–040735—MSD–062111–040773; MSD–R062111–040848—R062111–040887; MSD–R062111–068275—MSD–R062111–068309; MSD–R062111–040912—MSD–R062111–041018; MSD–R062111–068487—MSD–R062111–068541; MSD–R062111–079038—MSD–R062111–079039.

surgery: clinical and radiographic outcomes in anterior lumbar spinal fusion. *J. Bone Joint Surg. Am.* 2005; 87:1205–12.[27]

- Glassman SD, Dimar JR, Burkus K, et al. The efficacy of rhBMP–2 for posterolateral lumbar fusion in smokers. *Spine* 2007.[28]
- Dimar JR, Glassman SD, Burkus JK, et al. Clinical and radiographic analysis of an optimized rhBMP–2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. *J. Bone Joint Surg. Am.* 2009.[29]
- Burkus JK, Gornet MF. Six-Year Outcomes of Anterior Lumbar Interbody Arthrodesis with Use of Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein–2. *JBJS* 2009.[30]
- Dawson E, Bae HW, Burkus JK, et al. Recombinant human bone morphogenetic protein–2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation. A prospective randomized trial. *J. Bone Joint Surg. Am.* 2009.[31]

Medtronic told the Committee that it instituted policies, beginning in the mid-2000s, to ensure that interactions between the company and physician authors regarding peer-reviewed publications are "appropriate."[32] These policies include:

- Prohibiting the compensation of "a researcher to speak about or broadly disseminate research findings prior to FDA approval of the unapproved uses, other than providing a report of publishable quality to Medtronic and/or a peer reviewed journal for publication."—implemented in April 2006.
- Requiring "that clinical trial outcomes be presented without bias and with full disclosure."—implemented on January 8, 2008.
- Requiring "that a Medtronic employee's contribution to any publication must be appropriately disclosed, according to the standards of the International Committee of Medical Journal Editors ("ICMJE")."—implemented in 2009.
- Barring "Sales and Marketing personnel from participating in a publication project as an author or contributor. Only employees in the Clinical, Medical Affairs, or Research and Development Departments were permitted to serve as authors or contributors (as defined by ICMJE Guidelines), and only with disclosure."—implemented on August 8, 2010.

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[27] See correspondence and draft articles MSD–R062111–034854—MSD–R062111–034894; MSD–R062111–034957—MSD062111–034994; MSD–R062111–061701—MSD–R062111–061708; MSD–R062111–064785—MSD–R062111–064787.

[28] See correspondence and draft articles MSD–R062111–065102—MSD–R062111–065120; R062111–065287—R062111–065317; MSD–R062111–043742—MSD–R062111–043775.

[29] See correspondence and draft articles MSD–062111–R065138—MSD–R062111–065155; MSD–R062111–043226—MSD–R062111–043246; MSD–R062111–056122—MSD–R062111–056142; MSD–R062111–037519—MSD–R062111–037546; MSD–R062111–046108—MSD–R062111–046160; MSD–R062111–067520—MSD–R062111–067566.

[30] See correspondence and draft articles MSD–R062111–058250—MSD–R062111–058285; MSD–R062111–045886—MSD–R062111–045954; MSD–R062111–046823—MSD–R062111–046900; MSD–R062111–037797—MSD–R062111–037821; MSD–R062111–047304—MSD–R062111–047332; MSD–R062111–060896—060898; MSD–R062111–049092—MSD–R02111–049100.

[31] See correspondence and draft articles MSD–R062111–059388—MSD–R062111–059410; MSD–R062111–060390—MSD–R062111–060421.

[32] Letter from Medtronic to the Senate Finance Committee, May 1, 2012; Medtronic policies, MSD–R021612–000187—MSD–R021612–000435.

- Prohibiting "Marketing personnel from making any contributions to the Discussion section of a publication, whether or not their contribution rises to the level of contributorship under ICMJE Guidelines" and prohibiting "any employees not identified as authors or contributors from contributing to the Discussion section."—implemented on October 11, 2011.
- Requiring that "all authors sign a standardized authorship agreement clarifying (1) the authors' responsibility to fully disclose relationships with Medtronic in any related publication, (2) the authors' responsibility to ensure appropriate attribution of authorship and contributorship, and (3) the authors' acknowledgement that Medtronic will not compensate physicians for writing or editing activities."—implemented on December 6, 2011.

The company defends collaboration between company employers and physician authors as "a well-established and widely-accepted part of the peer review process used to subject articles to critical scrutiny, as a medical device company like Medtronic typically maintains the most complete set of data relating to the use, as well as properties of its devices and thus is uniquely positioned to make valuable contributions to potential articles."[33] Further, Medtronic maintains that "the content of these articles is ultimately controlled by the authors."[34] The company wrote:

> Some of the employees who reviewed these articles resided nominally in the "Marketing" Department, but these employees generally are technically and scientifically trained who have earned doctoral or other advanced degrees in relevant disciplines and draw on deep expertise in the science of bone morphogenetic proteins, in the design and implementation of clinical studies, in technical expression of clinical practice, and in statistical analysis. Importantly, at [Medtronic Spinal Biologics] the Marketing Department is distinct from the Sales Department. Marketing personnel are tasked with, among other things, anticipating the needs of Medtronic's physician customers, following the latest scientific and clinical developments in the field, and using evidence to obtain wider approvals, use, and acceptance of products. Sales personnel, on the other hand, are designated to interact directly with customers for the purpose of effecting sales. In every case, however, physicians—not Medtronic personnel—prepare draft manuscripts, select content, approve suggested modifications, and are responsible for the final article content that they submit for publication and review by the scientific community.[35]

Medtronic Recommended Omitting Discussion of Adverse Events Possibly Associated With the Product in a 2005 Publication

According to the FDA's Summary of Safety and Effectiveness Data of the 2002 IDE InFuse product, "the incidence of adverse

[33] *Id.*
[34] *Id.*
[35] *Id.*

events that were considered device related, including implant displacement/loosening, implant malposition and subsidence were all greater in the investigational groups [that received InFuse] compared to the control group."[36] However, documents indicate that a Medtronic employee involved in editing a draft of the 2005 *Journal of Bone and Joint Surgery (JBJS)* article by Burkus, et al. about a similar InFuse procedure involving allograft bone (a cage made from donated bone rather than the FDA-approved titanium), recommended that "significant detail" concerning adverse event data should not be published.[37]

On June 16, 2004, Dr. Julie Bearcroft, Director of Technology Management in Medtronic's Biologics Marketing Department, wrote an e-mail to other Medtronic employees, commenting on a draft of the study, "I have made some significant changes to this document (some at the request of Dr. Burkus) both in format and content."[38] In this e-mail, she asked: "How much information should we provide relative to adverse events? . . . You will see my [note] in the attached document but I don't think significant detail on this section is warranted."[39] The referenced note in the draft article stated: "I don't believe we want to report in the same manner as we do in IDE studies. I personally think it is appropriate to simply report the adverse events were equivalent in the two groups without the detail."[40] According to an internal e-mail, the adverse events were observed in the trial and formatted in a detailed table.[41] But following the advice of Bearcroft, this table of adverse events was not included in the published paper.[42]

On July 3, 2004, after Medtronic edited the paper, Dr. Burkus sent a draft to his co-authors writing that "this manuscript documents the superiority in clinical and radiographic outcomes with the use of rhBMP2 in a study population of only 133 patients."[43]

According to the Carragee et al. *Spine Journal* article published in 2011, the 2005 *JBJS* article "reported no complications, such as end-plate fracture, collapse, and implant migration associated with rhBMP–2 despite the clear radiographic findings in at least the one presented case."[44] The e-mail exchange indicates that, in addition to Medtronic editing the manuscript without attribution, the company was recommending that the article omit a complete accounting of adverse event data, including serious adverse event data that were already considered a documented concern by FDA in similar application.

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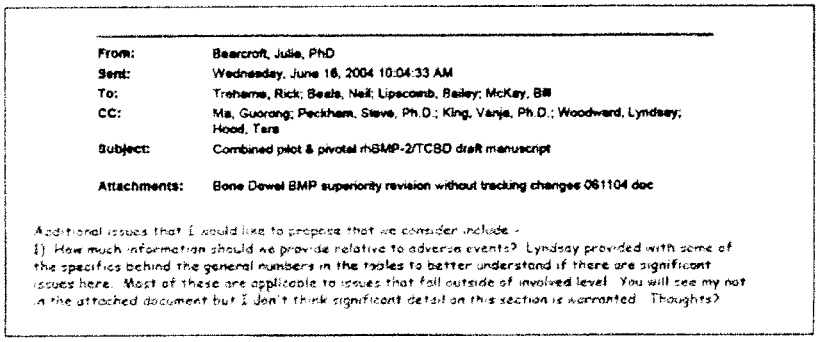
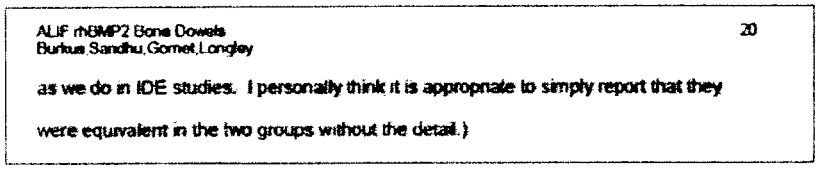
[36] FDA Summary of Safety and Effectiveness for InFuse Bone Graft/LT–Cage Lumbar Tapered Fusion Device, available at *http://www.accessdata.fda.gov/cdrh_docs/pdf/P000058b.pdf*.
[37] E-mail from Julie Bearcroft, June 16, 2004, MSD–R062111–034854.
[38] *Id.*
[39] E-mail from Dr. Burkus, July 3, 2004, MSD–R062111–034957.
[40] *Id.*
[41] E-mail between Medtronic Employees on June 7, 2004, MSD–R062111–064785.
[42] E-mail between Medtronic Employees on June 7, 2004, MSD–R062111–064785.
[43] E-mail from Dr. Burkus, July 3, 2004, MSD–R062111–034957.
[44] *The Spine Journal* 11 (2011) 471–491.



From: Bearcroft, Julie, PhD
Sent: Wednesday, June 16, 2004 10:04:33 AM
To: Treharne, Rick; Beals, Neil; Lipscomb, Bailey; McKay, Bill
CC: Ma, Guorong; Peckham, Steve, Ph.D.; King, Vanja, Ph.D.; Woodward, Lyndsay; Hood, Tara
Subject: Combined pilot & pivotal rhBMP-2/TCBD draft manuscript
Attachments: Bone Dowel BMP superiority revision without tracking changes 061104.doc

Additional issues that I would like to propose that we consider include -
1) How much information should we provide relative to adverse events? Lyndsay provided with some of the specifics behind the general numbers in the tables to better understand if there are significant issues here. Most of these are applicable to issues that fall outside of involved level. You will see my not in the attached document but I don't think significant detail on this section is warranted. Thoughts?



ALIF rhBMP2 Bone Dowels 20
Burkus,Sandhu,Gornet,Longley

as we do in IDE studies. I personally think it is appropriate to simply report that they

were equivalent in the two groups without the detail.)

These types of adverse events were disclosed in Table V of a 2009 follow-up article concerning the original IDE study.[45] Studies published in 2007 revealed that InFuse is associated with "a clinically important early inflammatory and osteoclastic effect of the rhBMP–2 in soft tissue and bone, respectively."[46] In other words, Medtronic recommended against including information in the study that was ultimately revealed to have an association between InFuse and weakening that could lead to collapse of the bone and implant and required that patients undergo additional surgery.

The CONSORT (Consolidated Standards of Reporting Trials) Group, an organization that develops guidelines for reporting randomized controlled trials endorsed by medical journals such as the *New England Journal of Medicine* and the *Journal of the American Medical Association,* recommended in its guidelines in 2001 that "[a]ll important adverse events or side effects in each intervention group" should be reported in the "Results" section of a publication of a randomized trial.[47] Although not in effect at the time Bearcroft made the recommendation, in 2004, the CONSORT group identified the practice of "providing summed numbers for all adverse events for each study arm, without separate data for each type of adverse event" as a "poor reporting practice."[48] The adverse events observed in the allograft trial were observed and formatted in a table, but following the advice of Bearcroft, the table was not included in the published paper.[49]

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[45] Burkus, et al., "Six-Year Outcomes of Anterior Lumbar Interbody Arthrodesis with Use of Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein–2," *JBJS* 2009.
[46] *The Spine Journal* 11 (2011) 471–491.
[47] Moher, et al., "The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials," *JAMA,* April 18, 2001.
[48] "Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement," *Ann. Intern. Med.,* 2004; 141:781–788 at *http://www.annals.org/content/141/10/781.full.pdf+html.*
[49] E-mail between Medtronic Employees on June 7, 2004, MSD–R062111–064785.

Medtronic Sought to Emphasize Pain in Alternative Treatments

Documents show that Medtronic edited draft publications to stress the pain patients experienced from undergoing a bone graft procedure instead of receiving InFuse. Medtronic markets InFuse as a less painful alternative to bone graft procedures for patients undergoing spinal fusion surgery. Medtronic's website states: "According to numerous studies, the harvesting procedure is actually more painful than the fusion itself, and nearly a third of patients experience hip pain two years following surgery. When compared to traditional spinal fusion procedures, INFUSE® Bone Graft, when used with the LT–CAGE® Device, eliminates the pain and blood loss, and reduces the amount of time spent in the hospital to treat complications resulting from the second site of surgery."[50]

However, spinal surgeons are beginning to question whether "the oft-cited 'painful iliac crest donor site' is less serious and frequent than BMP enthusiasts would have us believe" after a recent study showed that "[t]he incidence of pain over the iliac crest was similar in patients in which iliac crest was harvested and those in which no graft was harvested."[51]

After receiving a draft of an early InFuse study[52] to review in October 2001, Medtronic's Neil Beals, whose "primary job responsibility was to manage Biologics marketing programs and initiatives,"[53] recommended that the physician authors of the study emphasize pain experienced by patients who received the bone graft. The patients were divided into an investigative group that received InFuse and a control group that received a bone graft obtained from the iliac crest of their pelvis.[54] An October 31, 2001 e-mail shows that Beals suggested to Dr. Burkus that "a bigger deal should be made of elimination of donor site pain with INFUSE . . . so that 'equivalent' results aren't received as a let down."[55] Again, after reviewing a later draft of the study, Beals asked Dr. Burkus on March 8, 2002, "would it be appropriate to make a bigger deal out of donor site pain and include more discussion and references?"[56] Subsequently, a sentence was inserted at the end of a later draft, and included in the published version of the article, that read, "The use of rhBMP–2 is associated with high fusion

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[50] Medtronic INFUSE® Bone Graft + LT–CAGE® Lumbar Tapered Fusion Device Fact Sheet, *http://wwwp.medtronic.com/Newsroom/LinkedItemDetails.do?itemId=1101769224707&itemType=fact_sheet&lang=en_US.*

[51] Hu, Serena S., "Commentary: Illiac crest bone graft: are the complications overrated?" *The Spine Journal*, June 2011, *http://www.spine.org/Documents/TSJJune2011_Hu_Commentary.pdf;* Howard et. al., "Posterior iliac crest pain after posterolateral fusion with or without iliac crest graft harvest," *The Spine Journal*, June 2011, *http://www.spine.org/Documents/TSJJune2011_Howard_etal_PosteriorIliacCre.pdf.*

[52] "Anterior lumbar interbody fusion using rhBMP–2 with tapered interbody cages," *J. Spinal Disord. Tech.* 2002 Oct; 15(5):337–49, *http://www.ncbi.nlm.nih.gov/pubmed/12394656.*

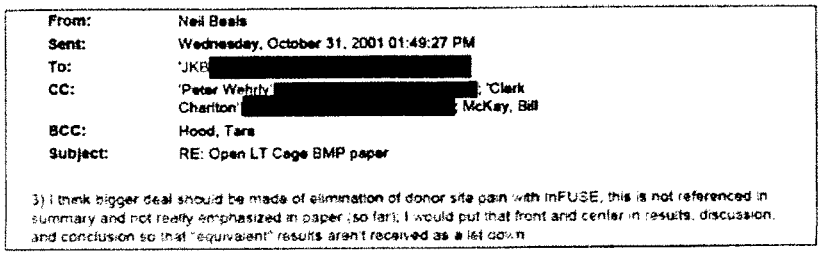
[53] Medtronic provided the Committee with this summary of Neil Beals's job titles and corporate responsibilities in a correspondence on May 5, 2012: "Neal Beals, M.S., M.B.A. is the former Vice President of Biologics Marketing, a position he held from February 2003 to August 2011. Mr. Beals joined Sofamor Danek in 1998 as Group Director, Tissue/Biologics within the Interbody Division. He held this position until October 2000 when he became Group Director, Biologics. He became Vice President of Biologics Marketing in 2003 and a Corporate Vice President in 2007. In these positions, his primary job responsibility was to manage Biologics marketing programs and initiatives."

[54] "Anterior lumbar interbody fusion using rhBMP–2 with tapered interbody cages," *supra* at 32.

[55] E-mail from Neil Beals to Dr. Burkus, October 31, 2001, MSD–R062111–033566.

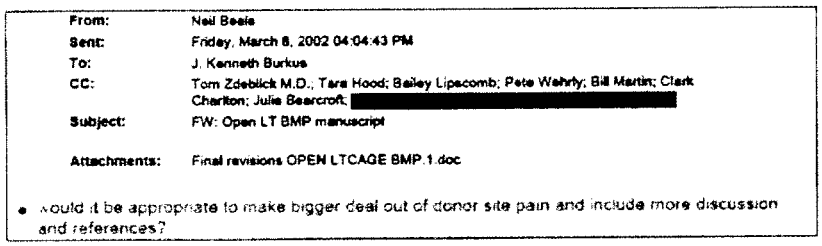
[56] E-mail from Neil Beals to Dr. Burkus, March 8, 2002, MSD–R062111–077880.

rates without the need for harvesting bone graft from the iliac crest and exposing the patient to the adverse effects associated with that procedure."[57]



From: Neil Beals
Sent: Wednesday, October 31, 2001 01:49:27 PM
To: 'JKB[redacted]
CC: 'Peter Wehrly'[redacted]; 'Clark Charlton'[redacted]; McKay, Bill
BCC: Hood, Tara
Subject: RE: Open LT Cage BMP paper

3) I think bigger deal should be made of elimination of donor site pain with INFUSE, this is not referenced in summary and not really emphasized in paper (so far); I would put that front and center in results, discussion, and conclusion so that "equivalent" results aren't received as a let down

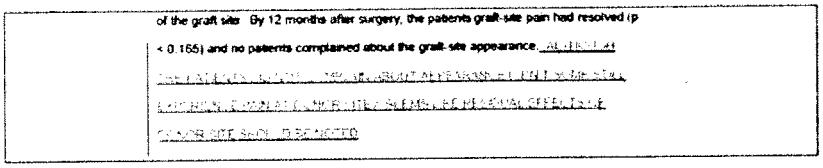


From: Neil Beals
Sent: Friday, March 8, 2002 04:04:43 PM
To: J. Kenneth Burkus
CC: Tom Zdeblick M.D.; Tara Hood; Bailey Lipscomb; Pete Wehrly; Bill Martin; Clark Charlton; Julie Bearcroft; [redacted]
Subject: FW: Open LT BMP manuscript
Attachments: Final revisions OPEN LTCAGE BMP.1.doc

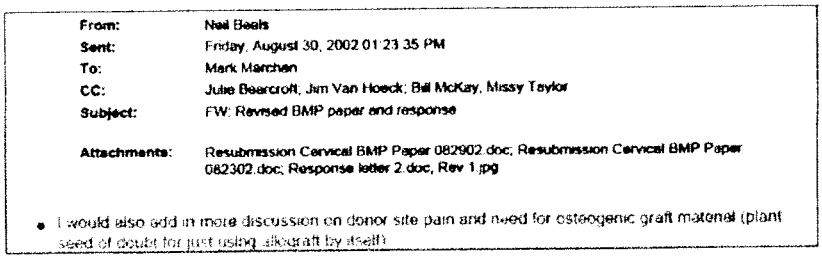
- Would it be appropriate to make bigger deal out of donor site pain and include more discussion and references?

Medtronic also sought to include discussion of long-term pain in the Baskin, et. al. 2003 paper on InFuse in the cervical spine. In a draft of the publication that was being circulated on August 30, 2002, the authors wrote, "[b]y 12 months after surgery, the patients [sic] graft-site pain had resolved . . . and no patients complained about the graft-site appearance." Beals inserted comments after this sentence stating, "ALTHOUGH THE PATIENTS DID NOT COMPLAIN ABOUT APPEARANCE DIDN'T SOME STILL EXPERIENCE PAIN AT THE DONOR SITE? SEEMS LIKE RESIDUAL EFFECTS OF DONOR SITE SHOULD BE NOTED."[58] [sic] [emphasis in original]. In an e-mail to his colleague, Beals wrote, "I would also add in more discussion on donor site pain and need for osteogenetic graft material (plant seed of doubt for just using allograft by itself)."[59] A review of the final published article reveals that, after Beals made the suggestion to emphasize pain at the bone graft site, a sentence was added in the final version of the article that read, ". . . even at the 24-month follow-up assessment, some patients continued to experience residual pain at the donor site, and rated the appearance of the site as only fair."

[57] Compare drafts attached to e-mails from Dr. Burkus to Neil Beils on March 8, 2002, MSD–R062111–078880, MSD–R062111–077882 and April 4, 2002, MSD–R062111–033863, MSD–R062111–033825.
[58] Draft copy of Baskin et. al. study e-mailed on August 30, 2002, MSD–R062111–034124.
[59] *Id.*



of the graft site. By 12 months after surgery, the patients graft-site pain had resolved (p < 0.155) and no patients complained about the graft-site appearance.



From: Neil Beals
Sent: Friday, August 30, 2002 01:23:35 PM
To: Mark Marchan
CC: Julie Bearcroft; Jim Van Hoeck; Bill McKay; Missy Taylor
Subject: FW: Revised BMP paper and response
Attachments: Resubmission Cervical BMP Paper 082902.doc; Resubmission Cervical BMP Paper 082302.doc; Response letter 2.doc; Rev 1.jpg

- I would also add in more discussion on donor site pain and need for osteogenic graft material (plant seed of doubt for just using allograft by itself)

Medtronic Attempted to Downplay Cervical Spine Side Effects in a 2006 Publication

In 2008, "the FDA issued an alert after receiving reports of life-threatening complication following cervical fusion procedures involving [bioengineered proteins such as InFuse], including breathing difficulty and swelling of the neck."[60] Additionally, a study published in the *Journal of the American Medical Association* found that "[p]atients who received a bioengineered protein during spinal fusion procedures to correct neck pain had far more complications than patients who did not get it."[61]

E-mails show that Rick Treharne, Senior Vice President of Clinical and Regulatory Affairs at Medtronic, unsuccessfully attempted to tone down a study SPINE published in 2006 that found a "significant rate of complications . . . after the use of a high dose of [rhBMP–2] in anterior cervical fusions." In December 2004, Rick Treharne e-mailed a co-author of this study, Dr. Glassman, in an unsuccessful attempt to have some of the critical language in the study modified. Treharne wrote, "Again it is probably too late, but page 14 line 13 says 'The high complication rate is alarming and warrants intense scrutiny.' I think what you are trying to say is that the occurrence [sic] adverse events (not effects as in the title) in these patients was higher than expected and warrants further investigation."[62] The e-mail from Treharne was sent after the paper was submitted to SPINE.

[60] "Bone-Growth Problems Show Risk in New Study," *New York Times*, June 30, 2009.
[61] *Id.*
[62] E-mail from Rick Treharn to Steve Glassman, December 15, 2004, MSD–R062111–035348.

From:	Treharne, Rick
Sent:	Wednesday, December 15, 2004 04:29:48 PM
To:	Steve Glassman (E-mail) [redacted]
Subject:	Article Reminder

Again it is probably too late, but page 14 line 13 says "The high complication rate is alarming and warrants intense scrutiny." I think what you are trying to say is that the occurrence adverse events (not effects as in the title) in these patients was higher than expected and warrants further investigation.

Additionally, even after Medtronic attempted to include a warning about cervical swelling on the FDA label, one Medtronic physician consultant recommended against raising alarms with the physician community. On April 8, 2004, Rick Treharne e-mailed Medtronic physician consultant Scott Boden, informing him that the company received complaints related to off-label use of InFuse in the cervical spine.[63] Dr. Boden responded that he was aware of a case of swelling where there was a "golf ball size mass in the neck clearly visible through the skin."[64] Boden recommended that surgeons needed to be continually warned about off-label use of BMP in the cervical spine.[65] Medtronic told the Committee that during this time, it voluntarily sought changes to the InFuse product label in June 17th, 2004 to notify the public of a risk of swelling when used in the cervical spine, but the effort was opposed by the FDA due to the agency's concern that adding a warning to the label about an off-label use was a form of off-label promotion. In June 2004, Rick Treharne wrote to Dr. Burkus that, based on his statistical analysis of new cases versus what was observed in the clinical trials, he did not, "at this time, see anything to worry about."[66] In August 2004, despite Dr. Boden's recommendation to Rick Treharne earlier that year that physicians should be "continually warned" about off-label use, Dr. Boden told Dr. Charles Mick of the North American Spine Society that because there wasn't enough information to identify the cause of the swellings, "it may be premature for any 'official' warning."[67] Medtronic paid Dr. Boden $705,457 through 2004 and $28,796,034 by the end of 2008. FDA granted Medtronic permission to send a "Dear Doctor" letter to physicians conveying concerns about InFuse on September 14, 2004 and placed a warning on the product label on December 7, 2004.

Omission of Retrograde Ejaculation Rates in Investigative Patient Groups

In his 2011 *Spine Journal* article, Dr. Carragee reported that "multiple independent studies have found that the rate of [retrograde ejaculation (a condition that causes sterility)] in ALIF with rhBMP–2 is approximately 5% to 7% and possibly two to four times higher than the rate observed without rhBMP–2."[68] However, the physician authors who reported the clinical results of a major Medtronic-sponsored study in the *Journal of Spinal Disorders and*

[63] E-mail from Rick Treharne to Scott Boden, April 8, 2004, MSD–R062111–068997.
[64] E-mail from Scott Boden to Rick Treharne, April 10, 2004, MSD–R062111–068997.
[65] *Id.*
[66] E-mail from Rick Treharne to Dr. Burkus, June 14, 2004, MSD–R062111–069316.
[67] E-mail from Scott Boden to NASS President Charles Mick, August 16, 2004, MSD–R062111–069477.
[68] *http://www.spine.org/Documents/TSJJune2011_Carragee_etal_CriticalRev.pdf*, page 479.

Techniques attributed the adverse event to the surgical technique used without comparing the investigational study group receiving InFuse to the control group.[69] Dr. Carragee told the *New York Times* that the omission is significant because "[i]t is important that men who are considering having children have the opportunity to weigh the risks of the various available procedures."[70]

A February 2001 PowerPoint presentation indicates that Dr. Zdeblick was aware that retrograde ejaculation rates were higher in both investigational groups than the control group. In a PowerPoint presentation to study investigators in February 2001, Dr. Zdeblick reported a 10.3% rate of retrograde ejaculation using the laparoscopic technique, a 6.3% for patients who underwent an "open" technique, and a 1.5% rate for the control group. The 10.3% rate was noted in the presentation to be "[s]tatiscally different from [the] control [group]."[71]

Medtronic Wrote Author Responses to Peer-Review

E-mail exchanges between Dr. Burkus and Medtronic employees regarding a study of InFuse utilizing the posterior lumbar interbody fusion (PLIF) technique and published in *The Spine Journal* in 2004 demonstrates that Medtronic employees not only edited the draft manuscript to include comments supportive of InFuse, they also covertly participated in the peer-review process by drafting responses to peer-reviewers on behalf of the physician authors named on the paper.

On December 21, 2002, Dr. Burkus sent a draft manuscript of the study to Medtronic officials asking for assistance with "further data analysis."[72] Bill Martin, Vice President for Spinal Marketing, Global Communications, and Medical Education at Medtronic, made it clear to other Medtronic employees that Medtronic would be in a "supporting cast" in assisting Dr. Burkus with this study rather than reworking the paper.[73]

According to a January 1, 2003, e-mail written by Bill Martin, "Dr. Burkus wanted his name last (and all the neuro's first) so that it would be well accepted by the Neurosurgical community." In addition, Martin wrote that, "I'm sure none of us believe the PLIF *technique* is going to have a resurgence from this, but we may want to steer clear of calling it a flawed technique. There are still quite a few surgeons utilizing this technique and we probably don't want to put them in that position"[74] (emphasis in original).

In a January 10, 2003, e-mail to Dr. Burkus, Rick Treharne wrote, "In looking over the data, I was impressed with how well the BMP patients actually did. So much so that I added a few paragraphs at the end that you may not agree with." In the draft article, Treharne wrote:

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[69] *Id.*

[70] "New Study Links Spine Product From Medtronic to Risk of Sterility in Men," *New York Times*, May 25, 2011.

[71] PowerPoint presentation attached to a February 2, 2001 e-mail between Medtronic employees, MSD–R062111–032878; MSD–R062111–032916.

[72] E-mail from Dr. Burkus to Medtronic officials, December 21, 2002, MSD–R062111–040537.

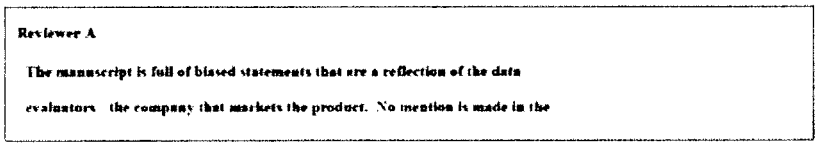
[73] E-mail from Bill Martin to Neil Beals and Peter Wehrly, January 1, 2003, MSD–R062111–078885.

[74] *Id.*

> In conclusion, this detailed, independent review of the results, which represent the first use of osteoinductive proteins in a PLIF procedure, are encouraging. These findings along with other studies for other indications imply that future larger PLIF studies with BMP–2 are needed. In future studies using modified surgical techniques, such as using more recessed cages to allow for extra posterior bone formation, adding steps to minimize bleeding, and/or adding secondary instrumentation may be beneficial. Further, possibly modifying patient selection, such as entering patients with less vertebral slip, may also help minimize confounding variables. All of these changes may produce even better, more convincing evidence that INFUSE Bone Graft can also be used as substitute for autograft in PLIF procedures.[75]

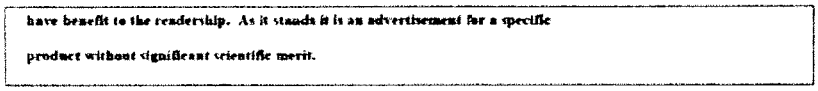
On February 1, 2003, Dr. Burkus e-mailed another draft of the BMP manuscript to Medtronic officials asking for "final comments."[76] On March 7, 2003, Julie Bearcroft e-mailed Dr. Burkus an updated version of this manuscript with her proposed changes to the draft.[77]

After submission of the initial draft of this study to *The Spine Journal*, physicians who peer-reviewed the article were critical of its presentation of the study results. One reviewer wrote: "Unless the authors can discuss the results of this study in an unbiased manner, which they have been unable to do in its present form, this data should not be published." Another reviewer wrote: "The manuscript is full of biased statements that are a reflection of the data evaluators—the company that markets the product." That reviewer recommended a discussion of potential bias in the text of the paper writing, "As it stands it is an advertisement for a specific product without significant scientific merit."[78]


Reviewer A

The manuscript is full of biased statements that are a reflection of the data

evaluators the company that markets the product. No mention is made in the


have benefit to the readership. As it stands it is an advertisement for a specific

product without significant scientific merit.

E-mail correspondence on May 28, 2003, indicates that Medtronic's Rick Treharne wrote and sent Dr. Burkus a draft letter to Dr. Tom Mayer, Editor-in-Chief of *The Spine Journal*, to address concerns raised by orthopedic surgeons tasked with peer-reviewing the submitted PLIF paper.[79] A subsequent e-mail by Julie Bearcroft notes that she and Dr. Burkus collaborated further on the re-

[75] E-mail from Rick Treharne to Dr. Burkus, January 10, 2003, MSD–R062111–068009.
[76] E-mail from Dr. Burkus to Medtronic officials, February 1, 2003, MSD–R062111–040735.
[77] E-mail from Julie Bearcroft to Dr. Burkus, March 7, 2003, MSD–R062111–040848.
[78] E-mail from Rick Treharne to Dr. Burkus, May 28, 2003, MSD–R062111–040930.
[79] *Id.*

sponse to the peer-reviewers of this study during a Lumbar Spine Study Group event.[80]

In response to the peer-reviewers' concerns about bias in the manuscript, the response letter seemingly misled *The Spine Journal* by stating that "To help eliminate any potential bias, only one of the co-authors was a clinical investigator—the other three were independent reviewers of all the data. Since these data are taken from a clinical IDE study sponsored by a company, only the company would have all the data in its database—data that is reviewed by FDA auditors. We don't believe any discussion of bias is needed for the text."[81] By the end of 2003, "independent reviewers" Dr. Haid and Dr. Burkus would have received $7,793,000 and $722,000 from Medtronic, respectively. This draft letter, written at least in part by Medtronic on behalf of Dr. Burkus, did not disclose the company's role in directly editing the paper nor did it disclose the magnitude of financial payments made to the supposed "independent reviewers."

Upon hearing the news that there would be an editorial by Dr. Neal Kahanovitz criticizing the PLIF study along with the paper, Medtronic Senior Vice President and President for Europe, Canada, Latin America, and Emerging Markets, Michael Demane wrote in an e-mail to Bill Martin, "this is going to hurt more than help because of the reviewers [sic] comments. Too late to turn back tho."[82] [sic]

PEEK Spacer Cervical Spine Study

Documents show that Medtronic unsuccessfully proposed that the FDA approve a less restrictive rule for when the company must suspend patient enrollment in a clinical study of InFuse used in the cervical spine for safety reasons.[83] According to a November 1, 2006, e-mail written by Medtronic's Senior Director of Medical and Regulatory Affairs Dr. Martin Yahiro, the company proposed a weaker rule because "it would be very difficult to pin [an adverse event] on INFUSE."[84] Yahiro explained that a rule required by the FDA based on "specific events with incidence rates . . . would stop the trial when it would be hard to say it WASN'T INFUSE" (emphasis in original.)[85] Medtronic's proposed rule, according to Yahiro, was written to allow the company to continue the trial even "if a patient has an [adverse event] like severe cervical swelling" because Medtronic "can honestly say that it is not possible to know that the cause is definitely INFUSE."[86] However, the FDA rejected Medtronic's proposal and required that the company adopt stricter rules based on specific adverse event rates in its final protocol.[87]

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[80] E-mail from Julie Bearcroft to Dr. Burkus, June 3, 2003, MSD–R062111–068487.
[81] E-mail from Rick Treharne to Dr. Burkus, May 28, 2003, MSD–R062111–040930 at 041013.
[82] E-mail from Michael DeMane to Bill Martin, March 9, 2004, MSD–R062111–079038.
[83] See documents relating to Medtronic's Investigational Device Exemptions application for a clinical trial of the Infuse Bone Graft/PEEK Interbody Spacer/Anterior Cervical Plate, MSD–R021612–000767—MSD–R021612–000790.
[84] E-mail from Dr. Martin Yahiro, November 1, 2006, MSD–R062111–073578.
[85] *Id.*
[86] *Id.*
[87] Section 6.24 of the InFuse Bone Graft/PEEK Interbody Spacer/Anterior Cervical Plate Investigational Plan Protocal, MSD–R021612–000791.

----- Original Message -----
From: "Yahiro, Martin, M.D." <[redacted]
To: <jkb[redacted]Desrochers, Debbie"
<[redacted]>; "Bearcroft, Julie, PhD"
<[redacted]>; "Seals, Neil" <[redacted]
Sent: Wednesday, November 01, 2006 6:24 AM
Subject: Re: Draft Stopping Rules 10_30_06.doc

> Thanks for your note. I think we're all on the same page regarding the ability to determine the exact cause of an event that could possibly be related to INFUSE (or just a result of cervical surgery). We agree it would be very difficult to pin it on INFUSE, which is exactly why we wrote the stopping rule that way. What we don't want is a rule that would have specific events with incidence rates, etc., that would stop the trial when it would be hard to say it WASN'T INFUSE. The way we wrote it, WE make the determination whether it was INFUSE-related. This way, if a patient has an AE like severe cervical swelling, we can honestly say that it is not possible to know that the cause is definitely INFUSE and therefore the study need not be stopped.

Expert Testimony to the FDA Written By Medtronic

E-mails indicate that Medtronic drafted Dr. Hallet Mathew's presentation to the FDA Advisory Panel in January 2002. Dr. Mathews told the FDA Advisory Panel during his presentation, "I have no direct financial interest in the product under review here today and am not being paid for my participation in this meeting."[88] The implication of that narrowly crafted disclaimer is that Dr. Mathew's testimony was independent. However, an e-mail from December 2001 shows that Medtronic worked with the public relations firm Ketchum on preparing Mathew's speech.[89] Medtronic told the Committee that Mathews was not compensated for any activity undertaken in January 2002.[90] But Medtronic did pay Dr. Hal Mathews under consulting arrangements with the company in 2001[91] and was hired by the company as the vice president of medical and clinical affairs in 2007.[92]

Conclusion

The Committee's investigation discovered troubling evidence that Medtronic officials influenced the content of articles in peer-reviewed scientific publications to present InFuse in the best possible light. As physicians depend on peer-reviewed literature when making clinical decisions, biased articles in professional publications that downplay potential risks and exaggerate the benefits of a product have the potential to put patients' lives at risk. The Medicare and Medicaid programs also rely on peer-reviewed medical literature when determining covered benefits and services. While collaboration between study authors and industry is necessary to publish the results of clinical trials, as the data being presented is often controlled by the company that sponsored the research, the resulting articles must be untainted by industry bias.

[88] Transcript, FDA Advisory Panel, January 10, 2002, *http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3828t1.htm.*
[89] E-mail from Ketchum to Barry Lipscomb, December 11, 2001, MSD-R062111-077826.
[90] Correspondence between the Committee and Medtronic on June 22, 2012.
[91] *Id.*
[92] "Report: Medtronic lawyer filed whistleblower suit," Minneapolis Star Tribune, September 25, 2008.

In order to address the problem of biased research in medical literature, drug and device manufacturers and journal editors need to implement stringent disclosure policies that detail industry funding to physician authors. In addition, medical journals should follow the example of *The Spine Journal* and critically examine past studies that may exhibit industry bias that harms patients and misleads physicians. Further, in the event that company employees are involved in the drafting of a scientific article, the employee should be listed as an author. Medtronic's revised policies governing proper interactions with physician authors are a step in the right direction. However, it is unlikely that this problem is limited to one company and a handful of medical journals and doctors. Medical device manufacturers, pharmaceutical companies, and other health care stakeholders should ensure that they have transparency along with strict rules preventing improper interactions between their employees and study authors. Medical journals, if they are to remain credible, must aggressively require contributors to disclose all ties to industry and any assistance they received in preparing the manuscript.

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

LIGIA VANESSA CHAPETON and GARY SEYMOUR, Plaintiffs, -against- MEDTRONIC INC., MEDTRONIC SOFAMOR DANEK, USA, INC., and ROGER HARTL, M.D, Defendants.	:	Civil Action No. _____

DEFENDANT ROGER HARTL, M.D.'S NOTICE OF CONSENT TO REMOVAL

Defendant Roger Hartl, M.D., by and through his undersigned counsel, hereby consents to the removal of this action from the Supreme Court of the State of New York, County of New York to the United States District Court for the Southern District of New York.

Dated: February 10, 2014.

Respectfully submitted,

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